

# **Norbornyl $\alpha$ -Diketones as Important Building Blocks in Organic Synthesis**

*A Thesis Submitted  
In Partial Fulfillment of the Requirements  
For the Degree of*

**DOCTOR OF PHILOSOPHY**

*by*

**Jyotirmayee Dash**

*to the*

**DEPARTMENT OF CHEMISTRY  
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दुखोत्तम विभा केचकर पुस्तकालय  
भारतीय प्रौद्योगिकी संस्थान कानपुर  
अवधि क्र० A.145023



A145023

**Dedicated  
to  
My Beloved Parents  
and Teachers**

“Purnamadah Purnamidam  
Purnat Purnamudchyate  
Purnasya Purnnamaday  
Purnameba Basisyate.”

(One whole is that, whole (too) is this;  
from whole, whole cometh; take whole  
from whole, whole remains.)



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## STATEMENT

I hereby declare that the matter embodied in this thesis entitled “Norbornyl  $\alpha$ -Diketones as Important Building Blocks in Organic Synthesis” is the result of investigations carried out by me in the Department of Chemistry at Indian Institute of Technology, Kanpur, India, under the supervision of **Dr. Faiz Ahmed Khan**.

In keeping with the general practice of reporting scientific observations, due acknowledgement has been made wherever the work described is based on the finding of other investigators.

*Jyotirmayee Dash*  
I. I. T. Kanpur

**Jyotirmayee Dash**

December, 2002

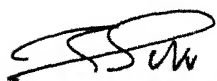
DEPARTMENT OF CHEMISTRY  
Indian Institute of Technology, Kanpur, India

CERTIFICATE

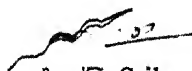
This is to certify that Jyotirmayee Dash has satisfactorily completed all the courses required for the Ph.D. programme at our department. These courses include:

CHM 602	Advanced Organic Chemistry I
CHM 614	Organic Photochemistry
CHM 631	Applications of Modern Instrumental Methods
CHM 662	Chemistry of Natural Products
CHM 664	Modern Physical Methods in Chemistry
CHM 681	Basic Biological Chemistry
CHM 800	General Seminar
CHM 801	Graduate Seminar
CHM 900	Post Graduate Research

Jyotirmayee Dash was admitted to the candidature of the Ph.D. degree in September 1999 after she successfully completed the written and oral qualifying examinations.

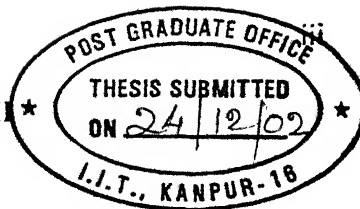


Prof. S. Sarkar  
Head  
Dept. of Chemistry  
I. I. T. Kanpur



Dr. K. Srihari  
Convener, DPGC  
Dept. of Chemistry  
I. I. T. Kanpur

CERTIFICATE



It is certified that the work encapsulated in this thesis entitled "Norbornyl  $\alpha$ -Diketones as Important Building Blocks in Organic Synthesis" has been carried out by Miss Jyotirmayee Dash, under my supervision and the same has not been submitted elsewhere for a degree.

(Dr. Faiz Ahmed Khan)  
Thesis Supervisor  
Associate Professor  
Department of Chemistry,  
I. I. T. Kanpur, 208016

Kanpur  
December, 2002

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I express my deep sense of gratitude to my father Basant Kumar Dash and mother Puspa Mishra for their enormous amount of patience and sacrifices, love and prayer, encouragement and support; which today make me existence. I take this opportunity to express my immense respect to my parents, being my ideal teachers in school. Today it is for this reason I dedicate this piece of work with love and respect to my parents and all my teachers. My most affectionate younger brother Barada and sister Yajnaseni, whose confidence and faith for me motivate to work and provide moral strength and courage. I take this opportunity to express my immense respect to my grand fathers and mothers, all our family relatives and friends for their blessings and well wish.

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**Jyotirmayee Dash**

## SYNOPSIS

Name of the student: **Jyotirmayee Dash**

Roll No.: **9810777**

Degree for which submitted: **Ph.D.**

Department: **Chemistry**

Thesis title: **Norbornyl  $\alpha$ -Diketones as Important Building Blocks in Organic Synthesis**

Thesis Supervisor: **Dr. F. A. Khan**

Month and year of thesis submission: **December 2002**

The thesis has been organized under nine main sections, titled: a) Introduction, b) Chapter I, c) Chapter II, d) Chapter III, e) Conclusion, f) Experimental Section, g) Selected Spectra, h) References, and i) Appendix: X-ray data which will be followed by a Chart, listing all new compounds prepared and reported in the thesis.

The norbornyl  $\alpha$ -diketones **1**, the title compounds of the thesis, having a powerful assembly of two adjacent carbonyl groups in a rigid bicyclic frame-work, with the availability of a wide range of substituents  $R^1$  and  $R^2$  of our choice, and the bridgehead halogens, could function as versatile building blocks that are suitable for cleverly designed synthetic maneuvers to achieve the desired targets. The norbornyl  $\alpha$ -diketones **1** were recently prepared in our laboratory by following a novel and remarkably efficient methodology by employing cat.  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$  and stoichiometric  $\text{NaIO}_4$  oxidation of the corresponding tetrahalonorbornyl derivatives.

It is interesting to note that the presence of halogens in tetrahalonorbornyl precursors is rather a compulsion than choice and a complete reductive dehalogenation is almost invariably followed in almost all the applications known so far. We perceived that if the reactivity pattern of the halogens were exploited in selective organic synthesis, it would prove as an important asset to the chemistry arising from these valuable derivatives. We have demonstrated, for the first time, the selective exploitation of bridgehead halogens for C-C bond formation at the bridgehead and the utility of vinylic halogens to obtain synthetically useful  $\alpha$ -diketones **1** with the retention of bridgehead halogens. The  $\alpha$ -diketones were exploited for the synthesis of novel and structurally diverse molecular entities as diagrammed in Chart 1.

The Chapter I, titled the  $\alpha$ -Diketones as Precursors for Cyclopentanoids has three subsections.

[A] **Synthetic Studies Towards Pentenomycin**: It is interesting to note that in the case of mono-endo substituted derivatives, the  $\text{H}_2\text{O}_2/\text{NaOH}$  cleavage of diketones promotes highly regioselective intramolecular  $\text{S}_{\text{N}}2$  reaction at the tertiary bridgehead carbon leading exclusively, after esterification with diazomethane, to the bicyclic lactones **2** (Chart 1). The methodology was successfully used for the preparation of fully functionalized cyclopentane derivatives **3** from the corresponding chloroderivatives. The stereoselective formation of the potential bridged lactones was fruitfully exploited for studies directed towards the synthesis of antibiotic pentenomycin **4**. We have

successfully developed a very short and stereoselective sequence for the synthesis of 2-hydroxy methyl 4-deoxy pentenomycin 5 and 2-hydroxymethyl pentenomycin derivatives 6 in 5 and 7 steps in an overall yield of 41.3% and 20.6% respectively starting from the tetrabromonorbornyl derivatives. The key feature of our synthesis was the C<sub>5</sub> quaternary and C<sub>4</sub> stereocentre are fixed at an early stage in a stereoselective manner starting from the versatile bicyclic lactone 2.

### [B] A Novel Radical Approach to Unusual Spiro-lactam :

This section deals with an elegant and serendipitously discovered synthesis of functionalized spirocyclic lactams via radical mediated C-C bond formation. The radical mediated, intermolecular bridgehead C-C bond formation of the versatile bridged lactones 2 with acrylonitrile followed by LAH reduction of the adduct 7 (chart 1) intriguingly leads to the formation of novel spiro-lactam building blocks 8.

### [C] A Short Synthetic Route to $\gamma$ - and $\delta$ -

**Cyclopentannulated Lactones:** From our group we have observed the cleavage of keto-hemiacetals derived from catalytic ruthenium oxidation of tetrahalonorbornene derivatives possessing endo-hydroxymethyl substituents, under  $\text{Pb}(\text{OAc})_4$  or alkaline  $\text{H}_2\text{O}_2$  conditions to reveal the  $\gamma$ -lactone fused cyclopentanoids. In continuation of our preliminary observation a systematic study was carried out to realize the cyclopentannulated  $\gamma$ -lactones making use of the persuasive advantages of the structural flexibility and stereochemical control offered by the tetrahalonorbornene derivatives. Further, the cleavage of diketones

bearing endo haloalkyl groups under alkaline  $H_2O_2$  conditions also furnished  $\gamma$ - and  $\delta$ -lactones thus providing a choice from a range of dienophile precursors (allyl alcohol or allyl halide or 4-bromo-1-butene) which contribute three and four carbons, respectively to the  $\gamma$  and  $\delta$ -lactone fused cyclopentanoid skeleton **9**. The cyclopentadiene derived monoadduct was also fruitfully employed in the synthesis of oxa-tetracyclic hemiacetals and acetals **10** and a diquinane based  $\gamma$ -lactone **11** (Chart 1), which could serve as a precursor for the construction of rigid biologically important diacylglycerol (DAG) analogs.

The **Chapter II** of the thesis depicts “**A Concise Synthesis of Novel Oxabridged Compounds.**” In this chapter we described the development of an elegant and stereoselective strategy for the replacement of 1,2-dihaloalkene bridge of tetrahalonorbornyl derivatives by an oxygen bridge via the  $\alpha$ -diketones, which allowed us to design some rigid molecular scaffolds that could act as smart molecules.

A highly oxygenated, novel pentacyclic bis-oxa-bridged compound **12** was synthesized with remarkable efficiency starting from readily available tetrachloro-5,5-dimethoxycyclopentadiene and 1,4-cyclohexadiene in 3 steps in an overall yield of 29.1% via one pot transformation of bis  $\alpha$ -dione. The *endo,syn,endo*- bis adduct of tetrachloro-5,5-dimethoxycyclopentadiene and cycloheptatriene was

exploited for the first time in organic synthesis for the construction of a novel bis-oxa-bridged pentacycle **13** via the bis diketone, having a core of *cis, syn, cis*- 5-7-5-ring system. We have successfully incorporated interesting structural variations in the structure of rigid molecular scaffolds; not only we can have highly symmetric molecules **12** and **13** with both the oxygen atoms on the same side (*syn*) but also "kinked structure" **14** and **15** with oxygen atoms on the opposite face (*anti*). We believe, this will have important consequences with regard to its structure and properties, e.g., now these molecules, although  $C_2$ -symmetric are chiral, a fact that could be fruitfully exploited to design chiral catalysts and phase transfer reagents. The molecule **15** has a perfect crown component with three oxygen atoms separated by two ethylene bridges, with the central oxygen suitably placed to participate in any binding or recognition event with either of the oxygen bridges present in opposite faces.

The *anti*-oxa-bridge derivatives **14** and **15** were prepared from 2:1 *endo,anti,endo*- Diels-Alder adduct of tetrachloro-5,5-dimethoxycyclopentadiene with cyclopentadiene and furan respectively. The stereochemistry of the bis adducts and the *anti* oxa-bridge derivatives were established by single crystal X-ray analysis of **14** and **15**. Interestingly, out of the three theoretical possible isomers only **16** was isolated in 80% of yield from the cleavage of pentacyclic bis-diketone derived from the  $RuCl_3$  oxidation of 2:1 adduct of cyclopentadiene. A single crystal X-ray analysis was carried out to unambiguously confirm the structure of **16**.

A variety of other oxa-bridge derivatives such as **17** ( $n=1-4$ ), a fully oxygenated cyclopentanoid core **18**, a molecule possessing a *cis* bis-THF core, (the dioxabicyclo [3,3.0] octane core) **19**, present in several naturally occurring lignans, were successfully synthesized. Further, the methodology was not restricted to only norbornyl  $\alpha$ -diketones derived from cyclic dienophiles, the bridged oxetane derivatives with any substituent pattern, for example **20** derived from monosubstituted  $\alpha$ -diketones were also prepared. In contrast to all the applications; the availability of 'retained' bridgehead halogens by our method, facilitate smooth incorporation of oxa-bridges in a stepwise manner through a formal 'bisnucleophilic' oxygen. The preparation of substituted diquinanes (one is shown in chart 1, **21**) and hydroazulene ring systems **22** were also realized from  $\alpha$ -diketones.

The **Chapter III** has two subsections, and describes "**Indium Mediated Reactions of Norbornyl  $\alpha$ -Diketones.**"

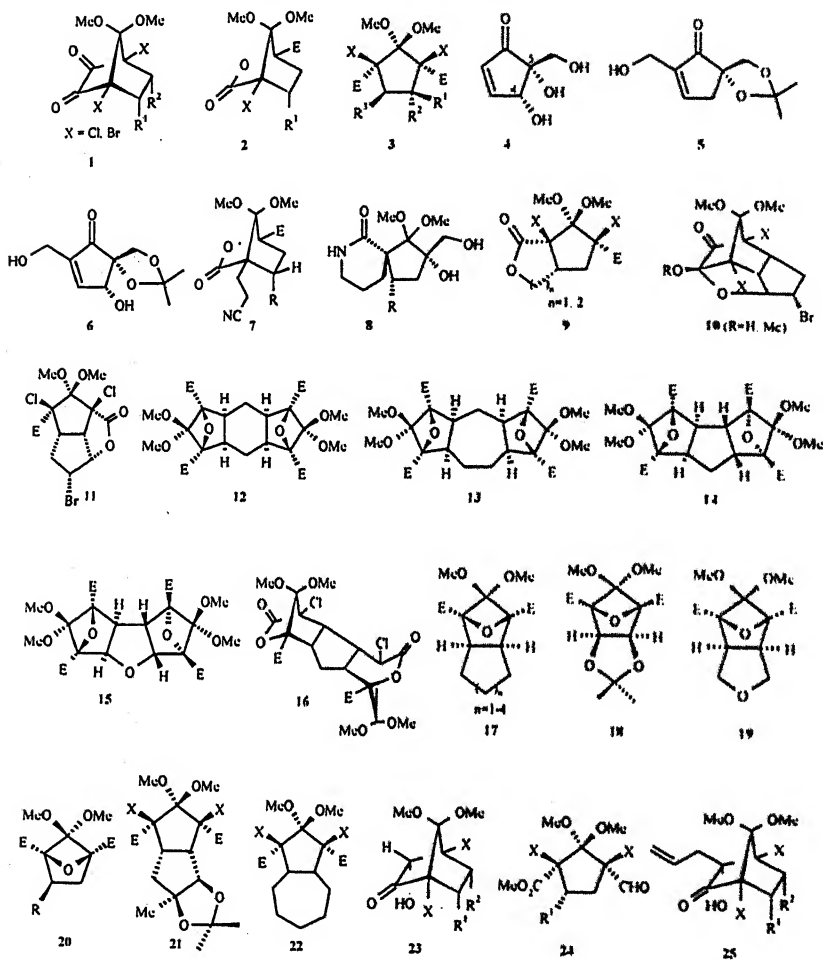
[A] **Regio- and Diastereoselective Reduction of Non-enolizable  $\alpha$ -Diketones to Acyloins Mediated by Indium Metal:** We developed an efficient methodology by which a variety of  $\alpha$ -Diketones were efficiently reduced with indium metal in methanol-water in the presence of either  $\text{NH}_4\text{Cl}$ ,  $\text{LiCl}$  or  $\text{NaCl}$  to give regio- and diastereoselectively the corresponding acyloins in good to excellent yield. The mono substituted derivatives underwent smooth transformation to the acyloins in a regio- and stereoselective manner to



furnish the major isomer **23** ( $R^2=H$ ) and the minor isomer **23** ( $R^1=H$ ) in a ratio of 100:0 to 64:36; probably via the protonation of the common acyloinate intermediate. In case of disubstituted derivatives indium mediated reduction proceeds stereoselectively to furnish the corresponding acyloins **23** in high yield. The cleavage of the acyloins under  $Pb(OAc)_4/MeOH-PhH$  condition provided a convenient and regioselective access to highly functionalized cyclopentane carboxaldehydes **24**, potential building blocks in organic syntheses.

**[B] Diastereoselection During Allylindium Addition to Norbornyl  $\alpha$ -Diketones:** We studied the allylindium addition to the norbornyl  $\alpha$ -diketones. In case of the disubstituted derivatives the indium mediated allylation proceeds stereoselectively to furnish the corresponding acyloins **25** in near quantitative yields. Interestingly, in monosubstituted derivatives ( $R^2=H$ ), the regioselectivity of allylindium addition depends on the chelation of the *endo*-substituent. The allylation of *endo* phenyl substituted diketone ( $X=Cl$ ) furnished 82:18 ratio of regioisomers, in which the major isomer was derived from the addition to the carbonyl group, which is diagonal to the *endo* substituent. However opposite regioselectivity was observed during the addition to *endo* alkoxy substituted derivatives.

**Chart 1:** The synthesis of novel and structurally diverse molecular entities starting from  $\alpha$ -diketones. ( $E=CO_2Me$ )



## List of Abbreviations

Ac	acetyl
AcOH	acetic acid
Ac <sub>2</sub> O	acetic anhydride
AIBN	$\alpha$ , $\alpha'$ -azobisisobutyronitrile
aq.	aqueous
Bn	benzyl
Bu <sup>t</sup>	tertiary butyl
cat.	catalytic
DMF	N,N-dimethylformamide
DMSO	dimethyl sulphoxide
eq.	equation
equiv.	equivalent
Et	ethyl
EtOAc	ethyl acetate
FVP	flash vacuum pyrolysis
h	hour(s)
h $\nu$	irradiation, photochemical reaction
LTA	lead tetraacetate
LAH	lithium aluminium hydride
Lit.	literature
Me	methyl
mp	melting point
PhH	benzene

quant.	quantitative
SET	single Electron Transfer
rt	room temperature
TBAT	tetrabutyl ammonium triphenyldifluoro silicate
THF	tetrahydrofuran
tlc	thin layer chromatography
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TBDMSCl	<i>tert</i> -butyl dimethylsilyl chloride
TBTH	tributyl tin hydride
Py	pyridine

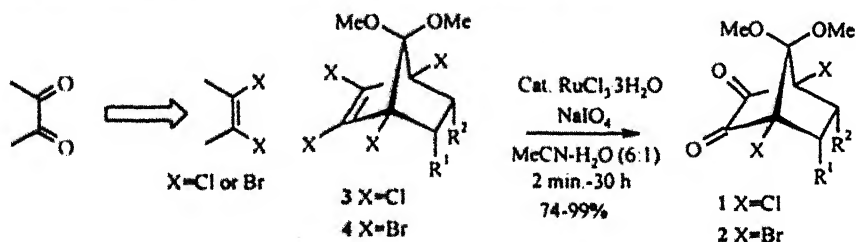
## General Introduction

The plenitude of functional groups along with the vast array of methodologies to create, interconvert and utilize them in a variety of bond forming and bond breaking reactions serve as an important asset for designing chemical synthesis of any target molecule. The carbonyl group received an overwhelming importance and quite often, played the pivotal role in the advancement of synthetic organic chemistry. The  $\alpha$ -diketones, a powerful assembly of two adjacent carbonyl functionality, are not surprisingly of great interest because of their wide ranging applications. The norbornyl  $\alpha$ -diketones 1,2, the title compounds of the thesis, having two adjacent carbonyl groups in a rigid bicyclic framework, with the availability of a wide range of substituents  $R^1$  and  $R^2$  of our choice, and the bridge head halogens, could function as versatile building blocks that are suitable for cleverly designed synthetic maneuvers to achieve the desired target. The norbornyl  $\alpha$ -diketones 1,2 were recently prepared in our laboratory by following a novel and remarkably efficient methodology by employing cat.  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$  and stoichiometric  $\text{NaIO}_4$  oxidation of tetrahalonorbornyl derivatives 3,4 (Scheme 1).<sup>1</sup>

In all the cases the reaction proceeds smoothly and efficiently, providing good to excellent yield of crystalline, yellow  $\alpha$ -diketones. The reaction time varied considerably, but in general tetrabromo derivatives required relatively longer time compared with tetrachloro

derivatives and so is the case with disubstituted versus monosubstituted ( $R^2=H$ ) derivatives in each series.

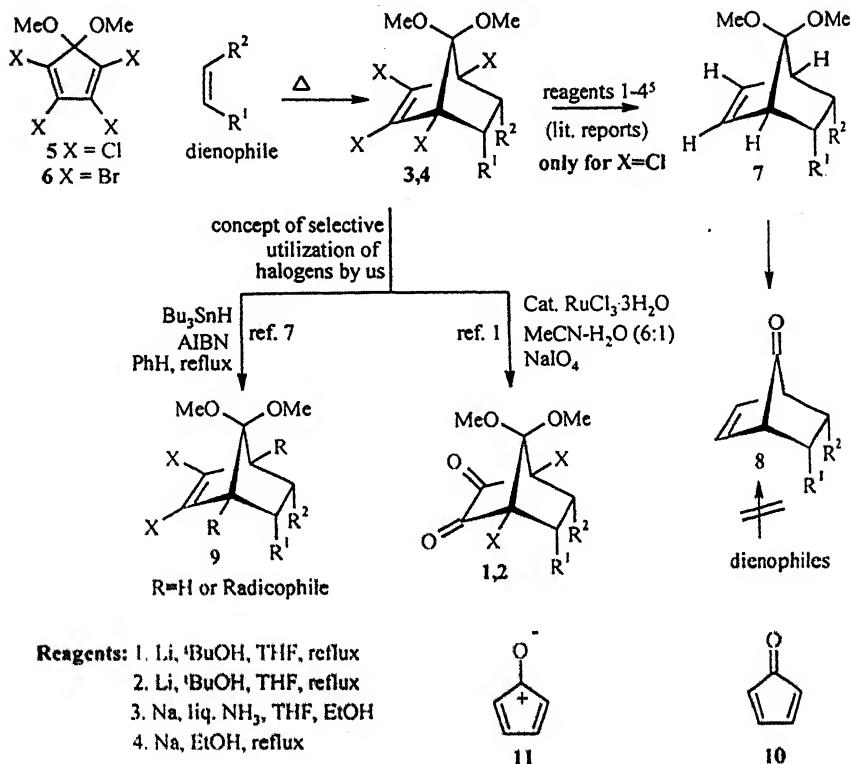
**Scheme 1:** Ruthenium-Catalyzed, Novel and Facile Procedure for the Conversion of Vicinal Dihaloalkenes to  $\alpha$ -Diketones<sup>1</sup>



Mono substituted derivatives  $R^2=H$ ,  $R^1=$  a) Ph, b) OEt, c)  $\text{CH}_2\text{OAc}$ , d) OAc, e) TMS, f)  $\text{CO}_2\text{Me}$ , g)  $\text{CH}_2\text{Br}$ , h)  $\text{CH}_2\text{Cl}$ , etc. Disubstituted derivatives,  $R^1=R^2=$  i-l)  $-(\text{CH}_2)_4-$ , m)  $\text{CO}_2\text{Me}$ , etc

The tetrahalonorbornene derivatives **3,4** the immediate precursors of the title compounds **1,2** are easily accessible via an atom economic and *endo*-selective Diels-Alder reaction between 1,2,3,4-tetrahalo-5,5-dimethoxycyclopenta-1,3-diene **5** (or **6**) and a suitable dienophile (Scheme 2).<sup>2,3</sup> The tetrachloro derivatives **3** continue to serve as inextricable, celebrated rigid templates in organic synthesis offering a high degree of regio- and stereocontrol.<sup>4</sup> The wide applications arising from these abundantly available and eminent rigid templates in the synthesis of complex multi-stereo natural products and their intermediates and marvelous unusual molecular architectures, are attributed to the presence of tunable functional groups, viz, masked 7-keto,  $\text{C}_2\text{-C}_3$  double bond and variable substituents acquired from dienophile.<sup>4</sup>

Scheme 2: Tetrahalonorbornyl derivatives in organic synthesis



It is interesting to note that the presence of four chlorine atoms is rather a compulsion than choice. All synthetic applications reported to date required a 7-norbornenone acetal 7 or the corresponding ketone 8 which are readily accessed from 3 by complete reductive dehalogenation<sup>5</sup> followed by acetal hydrolysis (Scheme 2). It is noteworthy that the role of tetrachloro diene 5 is to serve the purpose of a synthetic equivalent for cyclopentadienone 10 as the latter is unstable

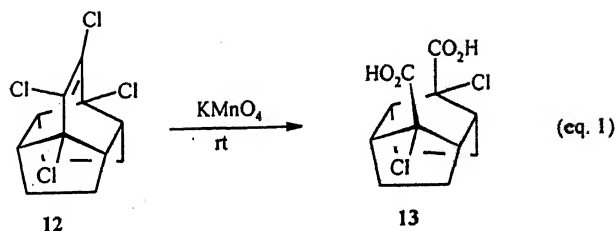
and highly susceptible to dimerization<sup>6</sup> because of the anti-aromatic character contributed by the polarized structure 11 involving  $4\pi e^-$  cyclopentadienium cation.<sup>6b</sup> Since 1,2,3,4-tetrachloro-5,5-dimethoxycyclopenta-1,3-diene 5 has been used as cyclopentadienone equivalent, the four chlorine atoms are therefore wasteful groups that are invariably stripped off subsequently in a reductive manner. Further, unlike tetrachloronorbornenes 3, the tetrabromo analogues 4, which could also be obtained easily via a Diels-Alder reaction,<sup>3</sup> did not receive any attention as useful building blocks. This, in our opinion, was due to lack of methods for selective utilization of the two sets (2 vinylic and 2 bridgehead) of halogens, while efficient methods exist for complete dehalogenation.<sup>5</sup> Any strategy that involves the complete reduction of halogens is quite uneconomical for the tetrabromo analogues 4 due to molecular weight loss that accompanies the process. The fact that the tetrabromo analogues were never exploited as building blocks in organic synthesis coupled with sturdiness of tetrachlorodimethoxynorbornene part of the cycloadducts towards a variety of reagents including organometallics, oxidizing and reducing agents, bases, and even acids, which diminished the fascination of these derivatives, provided us the stimulus to selectively exploit the 'strong'  $sp^2$  hybridized vinylic halides and 'susceptible'  $sp^3$  hybridized bridgehead halides. We perceived that if the reactivity pattern of the halogens in 3 and 4 is exploited in selective organic synthesis, it would prove as an important asset to the chemistry arising from these tetrahalonorbornene derivatives.



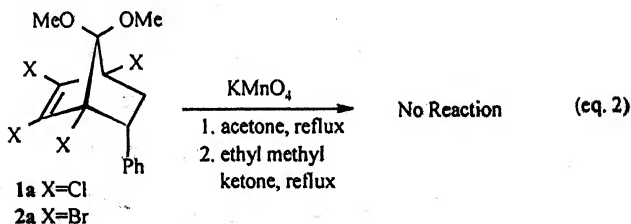
We have reported for the first time, the selective exploitation of bridgehead halogens for C-C bond formation at the bridgehead<sup>7</sup> and subsequently demonstrated the utility of vinylic halogens to obtain synthetically useful  $\alpha$ -diketones **1,2** with the retention of bridgehead halogens employing both tetrachloro and tetrabromo derivatives **3,4** in high yield.<sup>1</sup> Now we have accomplished the preparation of a small library of 55 new  $\alpha$ -diketones (Scheme 1). The reagent system, the 0.7 mol% of  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ , 1.6 equivalent of  $\text{NaIO}_4$  in 6:1 MeCN and water is found quite tolerable to a wide variety of substituents.<sup>1</sup>

This transformation was highly gratifying particularly in the light of literature search results which revealed that the vicinal dichloroalkene moiety in **3** is quite robust and inert to many oxidizing agents like  $\text{O}_3$ ,<sup>8a</sup>  $\text{OsO}_4$ ,<sup>9</sup>  $\text{KMnO}_4$ <sup>10</sup> etc. It is known that cyclic 1,2-dihaloalkenes can be cleaved by ozonolysis in MeOH<sup>11</sup> to give directly the methyl ester. Jung and coworkers<sup>8a</sup> observed that the exposure of tetrachlorodimethoxy-norbornene derivatives to ozone for several hours at room temperature (it is notable that ozonolysis reactions are normally performed at  $-78^\circ\text{C}$ ) in MeOH did not induce any reaction. The 1,2-dihaloalkene moiety on these systems was found to be unaffected by prolonged exposure to  $\text{OsO}_4$  for 2 days.<sup>9</sup>

The halogenated double bond cleavage in a relatively strain-free bicyclo[2.2.2] system was reported by Akhtar.<sup>10</sup> When the chloro alkene **12** was treated with  $\text{KMnO}_4$  in acetone, the double bond got cleaved to give the diacid **13** (eq. 1).<sup>10</sup>



We extended  $\text{KMnO}_4$  mediated oxidation method on our model substrates **1a** and **2a**. No change in the starting material was observed by treatment of **1a** and **2a** with  $\text{KMnO}_4$  in acetone at reflux temperature.<sup>1</sup> Both remained unreactive even under vigorous conditions of refluxing with ethyl methyl ketone (eq. 2). The literature precedents and our own findings reveal that the 1,2-dihalo alkene moiety of tetrahalo-7,7-dimethoxy norbornene is exceedingly robust and is inert to a wide range of strong oxidants.



The results presented in this thesis comprise some preliminary and interesting applications of these new derivatives **1,2** in organic synthesis. The dihalo norbornyl  $\alpha$ -diketones **1,2** were successfully used in the synthesis of naturally occurring molecules and important intermediates such as  $\gamma$ - and  $\delta$ -lactone fused cyclopentanoids<sup>12</sup> (Chapter 1), unusual molecules of novel architecture (Chapter 2),<sup>13</sup> and some organometallic transformations, particularly indium mediated efficient

regio- and diastereoselective reductions<sup>14</sup> and allylations taking the advantage of structural constraints of norbornyl skeleton were studied. The recognition of four halogens, to serve as fruitful functional groups and the concept of selective utilization lead us to employ the tetrabromo derivatives **4** to generate some interesting and purposeful chemistry.

The cleavage of the  $\sigma$ -bond between two carbonyl groups in  $\alpha$ -diketone derivatives paved the way to obtain a new class of cyclopentanoids or bridged bicyclic lactones. The potential bridged bicyclic lactones were successfully utilized in the synthesis of naturally occurring biologically active pentenomycin analogues, aza-spiro cyclic compounds (Chapter 1). Novel and structurally diverse molecular entities were efficiently synthesized utilizing the two methodologies developed in our laboratory<sup>1,7</sup> employing both tetrachloro- and tetrabromo-7,7-dimethoxynorbornene derivatives.

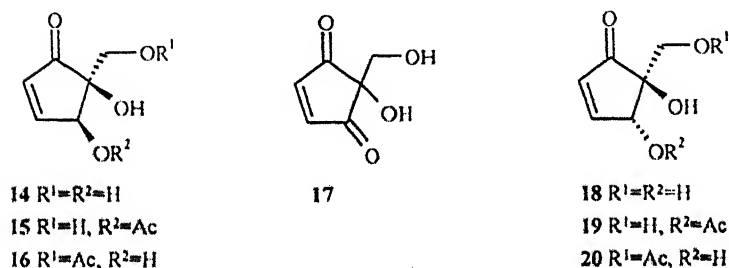
## Chapter 1A

### Synthetic studies towards Pentenomycins

#### 1. Introduction

Pentenomycins belong to a novel class of bioactive cyclopentanoid natural products. The seven members of small but rapidly growing family of antibiotics include Pentenomycin I, II and III (14, 15 and 16), dehydropentenomycin 17 and epipentenomycin I, II, and III (18, 19 and 20), shown in Chart 2.

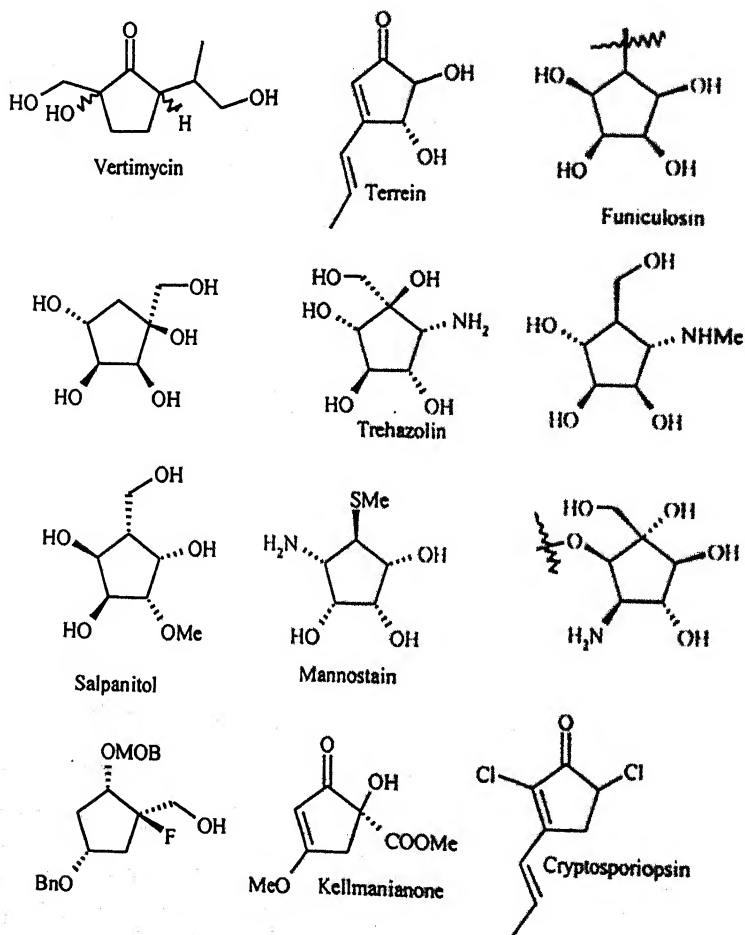
Chart 2: Seven members of pentenomycin family



The synthetic interests of various research groups towards these targets is due to their considerable activity towards Gram-positive and Gram-negative bacterial including *Neisseria gonorrhoeae*<sup>15,16</sup> and *Neisseria meningitidis*<sup>15,16</sup> and the potential pharmacological importance of the cyclopentenone structural entity, a highly reactive functionality in a wide variety of structurally complex antitumor agents.<sup>16</sup> The antibiotics, pentenomycin I (14), an amorphous powder and pentenomycin II (15), a syrup were first isolated in 1973 by Umino et al. from aerobically cultured broths of a mutant strain of *Streptomyces eurythermus*,<sup>11a</sup> the epipentenomycin I

(18) was isolated from carpophores of *Perziza* sp by Bernillon *et al* in 1989.<sup>15b</sup>

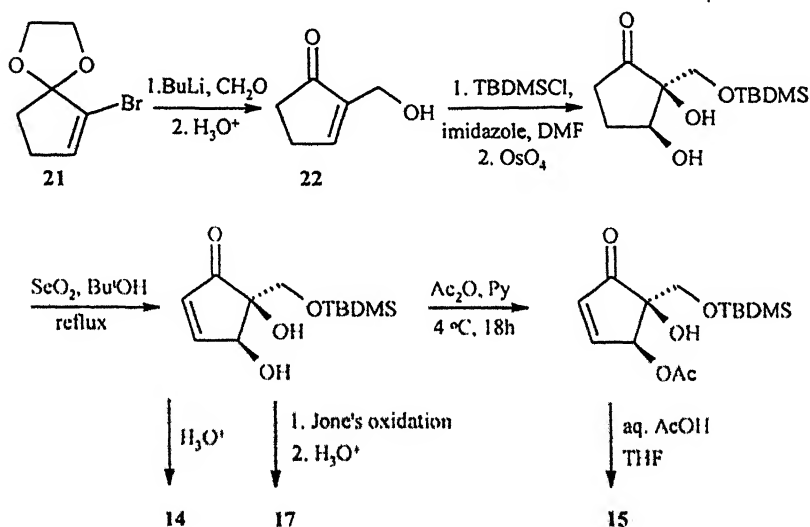
Chart 3: Polyhydroxylated cyclopentane derivatives



Among them, pentenomycin I 14, usually referred to simply as pentenomycin, attracted considerable attention and as a result four racemic and five chiral syntheses have been reported.<sup>17-23</sup> Various synthetic approaches given by different groups are discussed briefly

in the following section. The antibacterial antibiotic pentenomycins have been the subject of increasing attention because of their highly oxygenated basic skeleton, which was found in diverse range of biologically potent natural products.<sup>17-24</sup> Some of them are listed in Chart 3.

**Scheme 3:** Smith's synthesis of pentenomycins

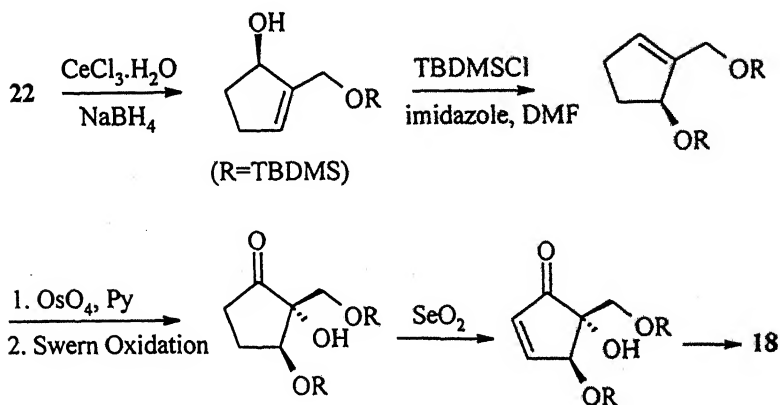


### 1.1. Various synthetic approaches to pentenomycins

**a) Smith's approach:** Smith and coworkers reported the synthesis of all the seven members of (±)-pentenomycin, utilizing α-keto vinyl anion equivalent.<sup>17</sup> The cyclopentenone **22** is the key and common intermediate in the synthesis which was obtained from α-bromoketals **21** (Scheme 3). Eventually the common intermediate **22** was derived from cyclopent-2-en-1-one.<sup>17a-c</sup> The epimeric series of

pentenomycins were also synthesized starting from **22** following the Scheme 4.<sup>17d,e</sup>

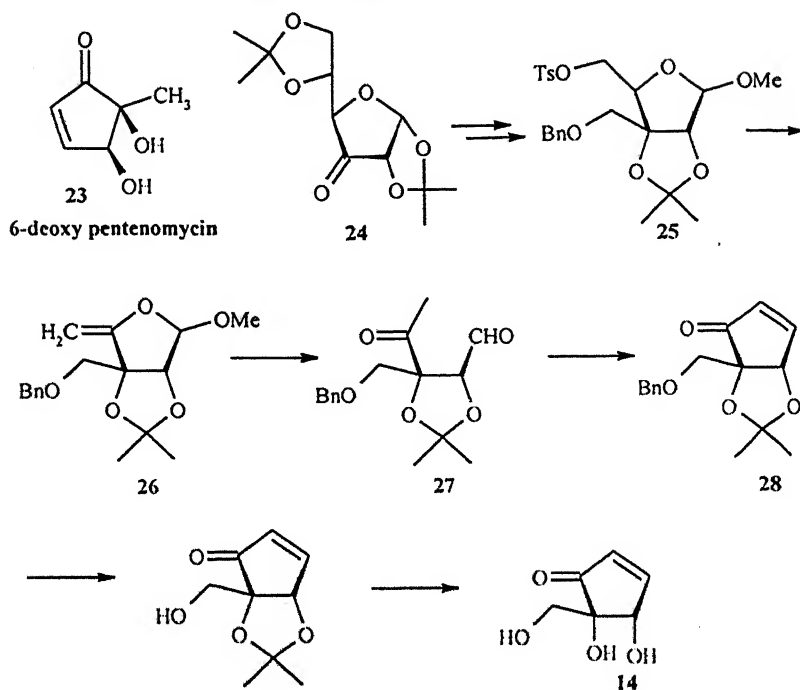
**Scheme 4:** Smith's synthesis of epipentenomycin



**b) Verheyden et al.'s approach:** Verheyden et al. described the first synthesis of optically active pentenomycin **14** and 6-deoxy pentenomycin **23** starting from D-glucose.<sup>18</sup> The 1,2:5,6-di-O-isopropylidene- $\alpha$ -D-ribo-hexofuranos-3-ulose derivative **24** was converted to vinyl ether **26** via **25**, which under mild acidic hydrolysis furnished **27**. The cyclopentenone **28**, the precursor for **14** was derived from the keto aldehyde **27** by an aldolisation-dehydration sequence (Scheme 5).

The authors concluded that "Even though the above synthesis highlights the versatility of carbohydrate derivatives as intermediates in the synthesis of optically active natural products but the synthesis is quite lengthy and associated with a number of unwanted problems."<sup>18</sup>

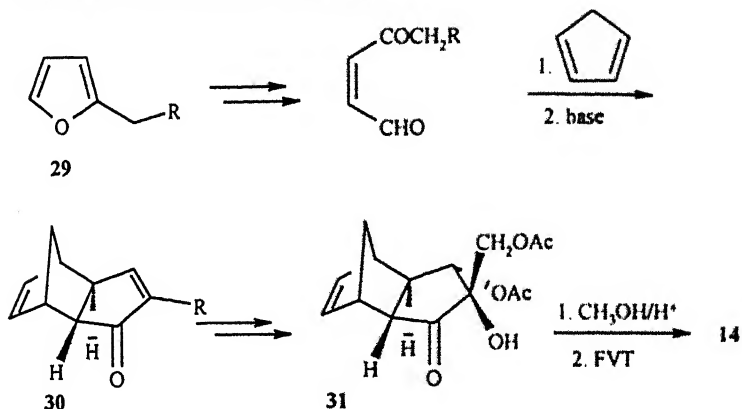
Scheme 5: Verheyden et al.'s synthesis of pentenomycin



c) **Zwanenburg's approach:** In this report the key intermediate, the 4-functionalised tricyclodecenone **30** was derived from a Diels-Alder cycloaddition between cyclopentadiene and a dienophile obtained from furan **29**. The tricyclodecenone **30** was transformed to diacetate **31**, which after acylation and Flash Vacuum Thermolysis (FVT) affords **14** in a cycloreversion reaction (Scheme 6).<sup>19</sup>

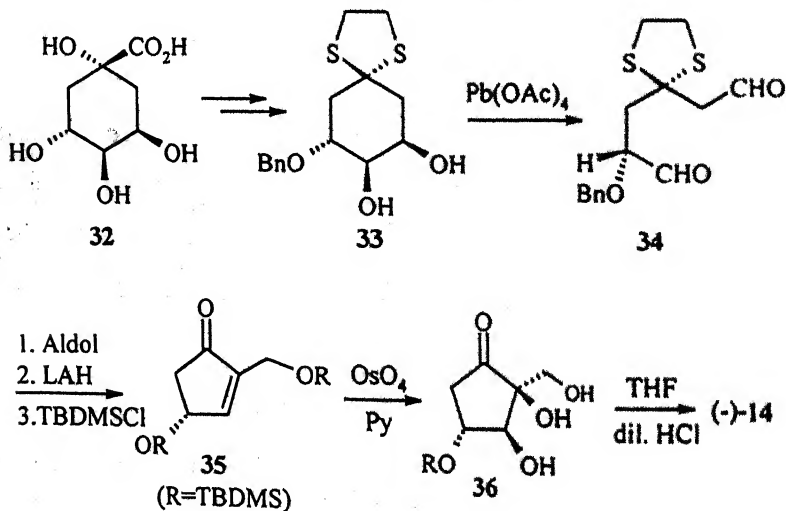


## Scheme 6: Zwanenburg's synthesis



d) **Stoodley's approach:** Stoodley and coworkers reported the synthesis of (-)- pentenomycin from D-quinic acid **32** and of (±)-pentenomycin from ethyl chloroacetate and chloroacetaldehyde.<sup>20</sup>

## Scheme 7: Stoodley's synthesis of (-)- pentenomycin

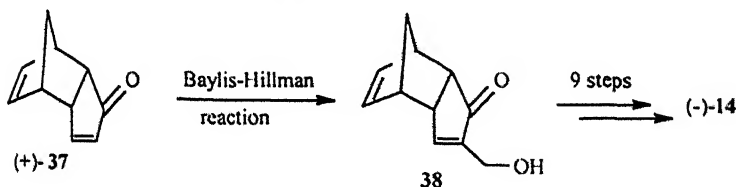


The D-quinic acid **32** was transformed to the diol **33**, which after oxidative cleavage affords the dialdehyde **34**. The cyclopentenone **35** was derived by an aldolisation-dehydration sequence, serves as the precursors for (-)- **14** via **36** (Scheme 7).<sup>20</sup>

In the above synthesis, none of the original stereo centers present in the starting material **32** was utilized, except one, which was employed to install the other functionalities of **14** and finally eliminated.

e) **Ogasawara's approach:** Ogasawara described a diastereocontrolled synthesis of (-)-pentenomycin<sup>21</sup> starting from (+)-**37**. The enantiopure **37** was converted to the key  $\alpha$ -hydroxy methylenone (+)-**38** by Baylis-Hillman reaction.<sup>21a</sup> The synthesis of (-)-**14** was completed by following a nine step sequence from **38**, involving thermolytic cycloreversion as the penultimate step (Scheme 8).<sup>21b</sup>

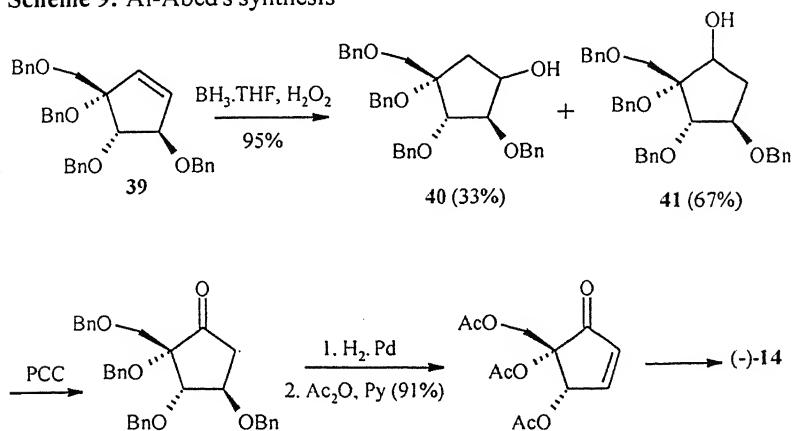
Scheme 8: Ogasawara's approach



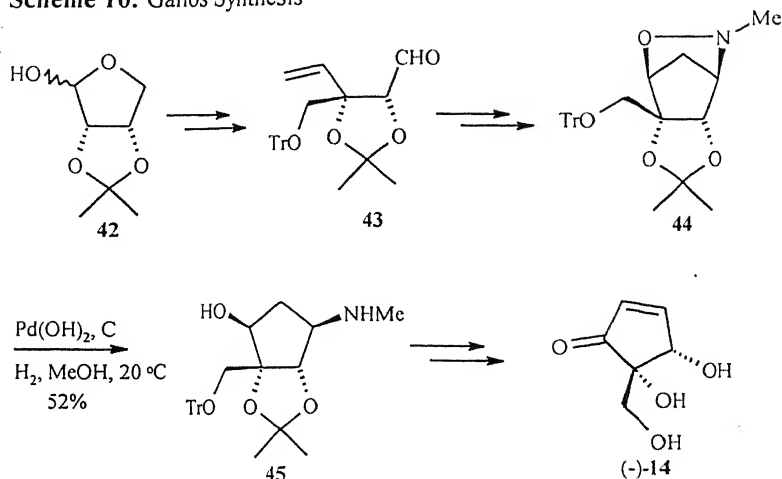
f) **Al-Abed's Approach:** Scheme 9 depicts a very recent synthesis of (-)-**14** by Al-Abed.<sup>22</sup> The synthesis was accomplished in five steps from the key intermediate polyhydroxylated cyclopentene

**39.**<sup>22a</sup> The intermediate **39** was prepared via a ring closing metathesis in 5 steps.<sup>22b</sup> The compound **39** was treated with  $\text{BH}_3\cdot\text{THF}$  to give the two regioisomeric alcohols **40** and **41** in a ratio of 1:2. The minor alcohol **40** was further elaborated to (-)- pentenomycin **14**.

**Scheme 9:** Al-Abed's synthesis

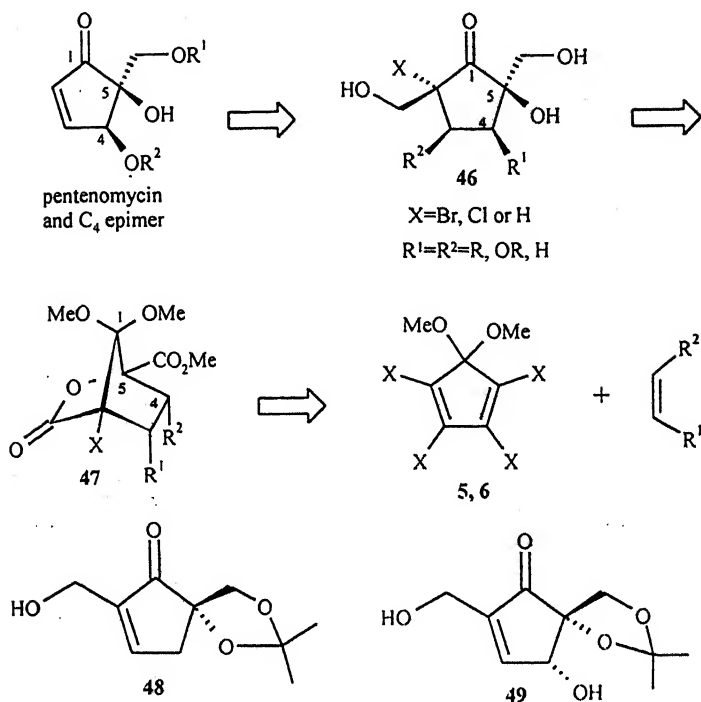


**g) Gallos' Synthesis:** Very recently Gallos reported the synthesis of pentenomycin starting from L-arabinose.<sup>23</sup> The L-arabinose was converted to the protected L-erythrose **42**, which was transformed to the  $\gamma$ -unsaturated aldehyde **43**. The key step involves the intramolecular nitronc cycloaddition of an intermediate derived from aldehyde **43** to reveal the cyclopentane ring **44**. The synthesis of **14** was achieved by reductive N-O bond cleavage in **44** and further oxidative deamination of the resulting aminocyclopentitol **45**.<sup>23</sup>

**Scheme 10:** Gallos Synthesis

**1.2. Our strategy:** The existing strategies towards pentenomycins could be categorized as, i) those starting from cyclopentanoid precursors, ii) those starting from cyclohexanoid precursors followed by transformation to cyclopentane derivatives via ring contraction protocols, and iii) those in which carbohydrates are transformed to carbocycles. Although there are a few methodologies to reach the antibacterial antibiotic, as reviewed above, but a simple, practical and efficient method is still required.

Scheme 11: Retrosynthetic analysis of pentenomycin

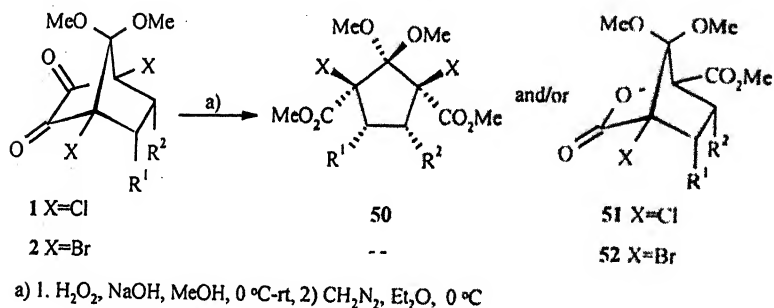


We envisioned a novel synthetic strategy, for the synthesis of pentenomycin **14**, based on recently developed concepts in our laboratory. The retrosynthetic analysis is depicted in Scheme 11. The key feature of our synthesis is to install the quaternary center (C-5) and C-4 in a stereoselective manner at an early stage starting from the bridged bicyclic lactone **47**, from which the advanced intermediate **46** could be derived. The C-5 quaternary center is also present in numerous cyclopentanoid natural products and carbocyclic nucleosides (Chart 3).<sup>24,25</sup> The bridged bicyclic lactones were easily derived from the  $\alpha$ -diketones. In this chapter, we have discussed the

regio- and stereoselective formation of bridged lactones 47 from the  $\alpha$ -diketones and its further utilization in a very simple, highly expeditious and efficient manner in the synthesis of 2-hydroxymethyl 4-deoxy pentenomycin derivative 48, and a 2-hydroxymethyl pentenomycin derivative 49, starting from the Diels-Alder cycloadducts 3,4 of readily available 1,2,3,4-tetrahalo-5,5-dimethoxy-cyclopenta-1,3-diene.

## 2. Results and Discussion

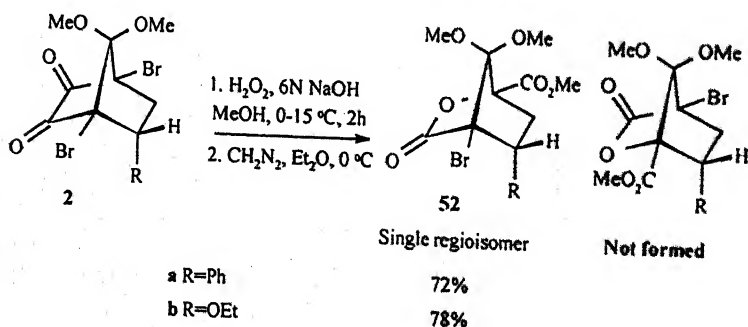
After successfully preparing a large number of  $\alpha$ -diketones in excellent yields (general introduction), we wanted to explore various possibilities for their application in organic synthesis. At first we focused our attention to cleave the sigma bond between the two carbonyl groups in order to generate highly functionalized cyclopentanoids. Our preliminary attempts using LTA in benzene at reflux temperature and  $\text{NaIO}_4$  in aqueous methanol were unsuccessful. Finally, subjecting the  $\alpha$ -diketones 1,2 to  $\text{H}_2\text{O}_2/\text{NaOH}$  conditions and subsequent esterification with diazomethane furnished the required cleavage products 50 and/or 51,52 (Scheme 12). We could successfully manipulate the reaction conditions to achieve exclusively either a new class of highly functionalized cyclopentanoids possessing bis( $\alpha$ -chloroester) groups 50, or the potential bridged bicyclic lactones 51,52.

Scheme 12: Cleavage reaction of  $\alpha$ -diketones

## 2.1. Regioselective access to bicyclic lactones

The most important aspect of the cleavage reaction is the question of regioselectivity in the case of monosubstituted  $\alpha$ -diketones 2a,b possessing bridgehead bromines (Scheme 13) under the cleavage reaction conditions optimized to obtain bridged bicyclic lactones. Interestingly, a single regioisomer of the bridged bicyclic lactones 52a,b were exclusively formed in good yields.

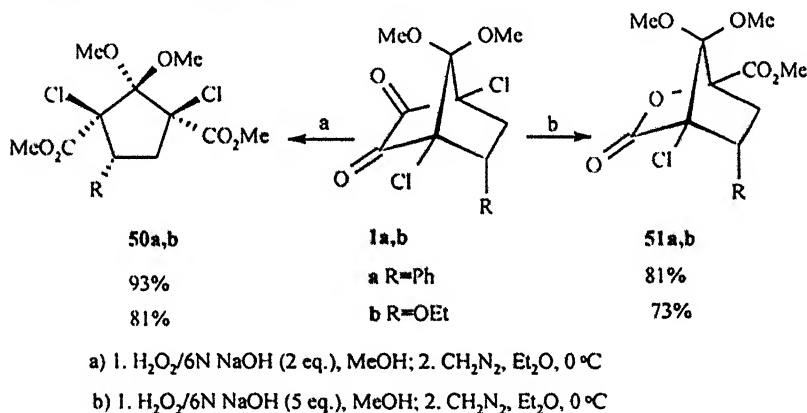
## Scheme 13: Regioselective access to bicyclic lactones



Scheme 14 shows the manipulation of experimental conditions to get exclusively either the functionalized cyclopentane

derivatives **50a,b** or the bicyclic lactones **51a,b** from chloro derivatives **1a,b**. Conducting the cleavage reaction of chloro derivatives **1a,b** with 2 equivalent of 6N NaOH for 2 h at 0-15 °C (identical conditions as for **2a** or **2b** which furnished bridged lactones), the cyclopentane derivatives **50a,b** were solely formed in excellent yields. However giving prolonged reaction time and 5 equivalent of 6N NaOH at room temperature, the bridged lactones **51a,b** were realized. Longer reaction time is required for chloro derivatives than the bromo analogues to prepare the bicyclic lactones.

Scheme 14: Cleavage reaction of chloro diketones

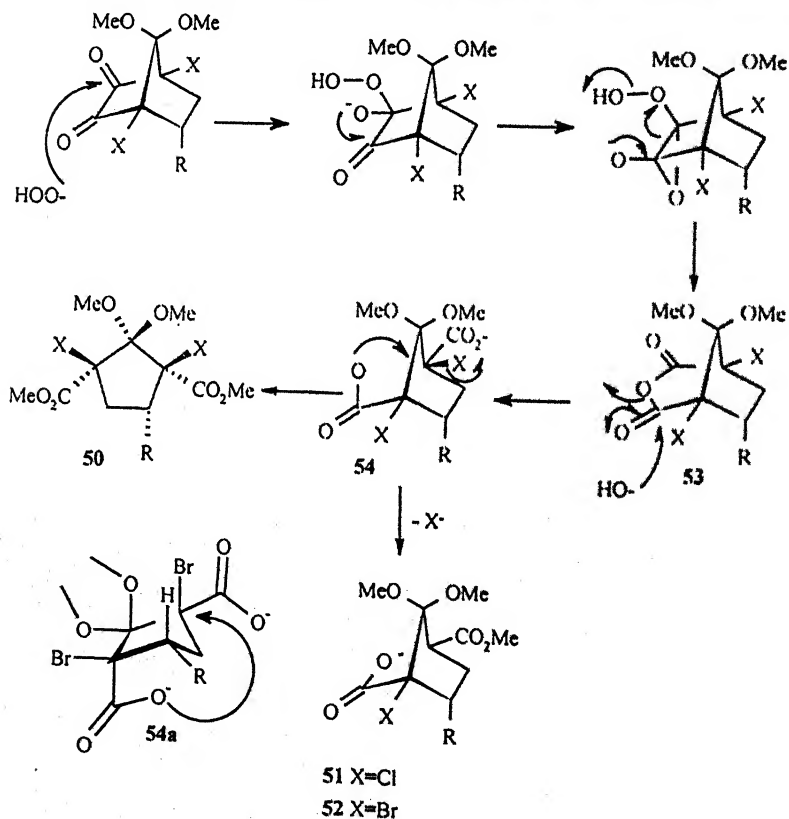


Scheme 15 depicts a plausible mechanism for the lactone formation. The initial anhydride intermediate **53**, which is expected to form upon treatment with alkaline  $\text{H}_2\text{O}_2$ , opens up under the basic reaction conditions to give the dicarboxylate **54**, a common intermediate for **50** or bridged lactones **51** and **52**. Acidic work-up followed by diazomethane esterification affords the cyclopentane



derivatives **50** from **54** (Scheme 15). On the other hand, it is interesting to note that under suitable conditions the dicarboxylate intermediate **54** resulting from the  $\text{H}_2\text{O}_2/\text{NaOH}$  cleavage undergoes highly regioselective intramolecular  $\text{S}_{\text{N}}2$  reaction at the tertiary bridgehead carbon leading exclusively, after esterification with diazomethane, to the bicyclic lactones **51** and **52**. This effect appears to be more pronounced in case of bromo derivatives **2**.

Scheme 15: Proposed mechanism for regioselective formation of lactone

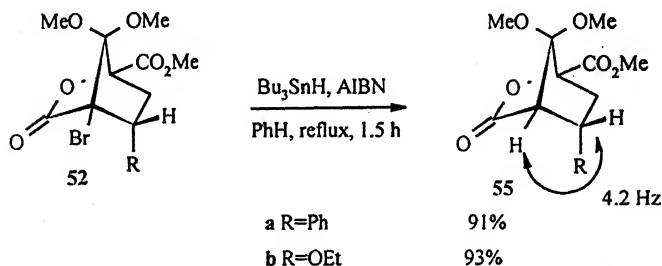


The carboxylate group, which is adjacent to the endo substituent cyclizes (shown in 54), to give a regioselective access to the bridged lactones. The origin of regioselectivity, in our opinion, is the reactive envelop conformer 54a in which the only unsubstituted methylene carbon prefers the 'flap' position while the R group occupies pseudo-equatorial position. This view is supported by molecular model analysis. In this preferred conformation, the carboxylate group  $\alpha$  to the substituent R and the bromide leaving group are suitably disposed for an intramolecular  $S_N2$  reaction (Scheme 15).

The  $^1\text{H}$  NMR spectrum of bromo lactones 52 showed three singlets (two for OMe and one for methyl ester) and the bromine-bearing bridgehead carbons appeared at 70.1 and 67.8 ppm respectively for 52a and 52b in  $^{13}\text{C}$  NMR spectrum. The bridgehead carbon bearing the ester group was assigned at 84.9 ppm for both 52a,b. Similarly for the chloro lactones 51a,b the chlorine-bearing bridgehead carbons showed at 77.7 and 78.3 ppm, and the carbon attached to the bridged esters appeared at 84.6 and 84.9 respectively. The IR spectrum of the compounds, 51 and 52 shows two peaks, at 1780-1800  $\text{cm}^{-1}$  for lactones and 1720-1740  $\text{cm}^{-1}$  for esters. The regiochemistry of 52 was unambiguously proved by hydrodebromination of the bridgehead halide using tributyltinhydride (TBTH/AIBN). The  $^1\text{H}$  NMR spectrum of the reduced compounds 55a,b showed a clear vicinal coupling between the bridgehead

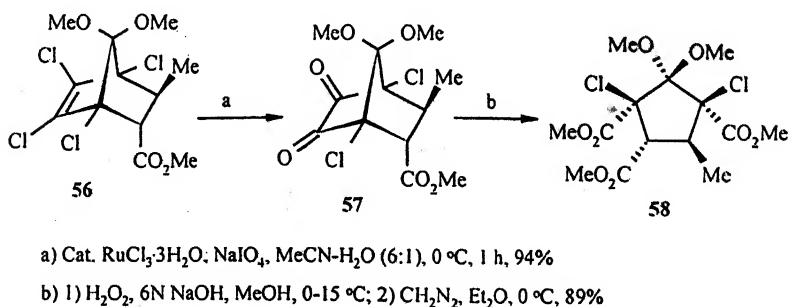
hydrogen and the *exo*-hydrogen ( $J = 4.2$  Hz) attached to the carbon bearing substituent R in both the cases (Scheme 16).

**Scheme 16:** Reductive hydrodebromination of bridged lactones



The methodology was successfully used to stereoselectively incorporate the substituents on the cyclopentane ring. For example, the diketone **57** obtained from the *endo* selective methyl crotonate adduct **56**, furnished exclusively a fully substituted cyclopentanoid derivative **58** (Scheme 17).

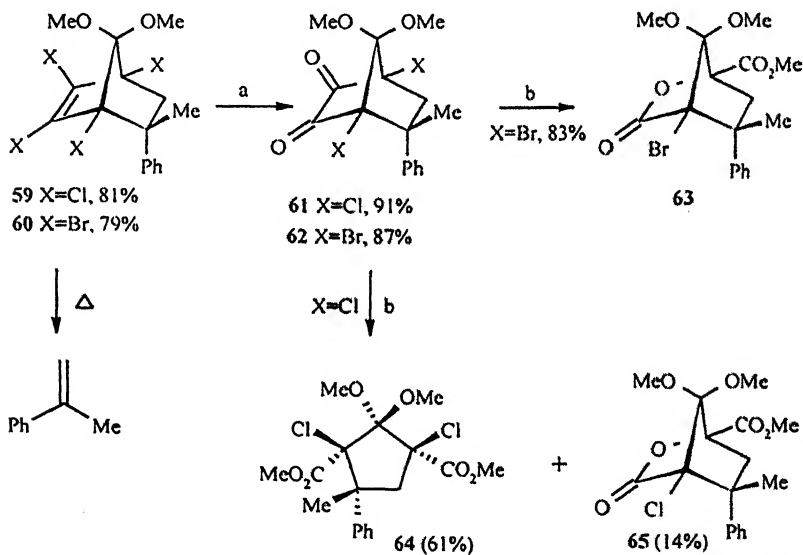
**Scheme 17:** Synthesis of a fully substituted cyclopentanoid **58**



Scheme 18 represents an example of a cleavage reaction of 5,5-disubstituted diketone. The Diels-Alder reaction between tetrahalo-7,7-dimethoxycyclopentadiene **5,6** and methyl styrene

furnished the adducts **59,60** in high yield (Table 1A.1, experimental section page no. 204). The adducts were oxidized to furnish excellent yield of the corresponding diketones **61,62**. The bromo diketone **62** upon cleavage gave exclusively the bridged lactone **63**. The cleavage reaction of the chloro analog, **61** afforded 61% of the cyclopentane derivative **64** having four contiguous quaternary centers. From the reaction mixture 14% of the bicyclic lactone **65** was also obtained (Scheme 18).

**Scheme 18:** Cyclopentanoids with four contiguous quaternary centers



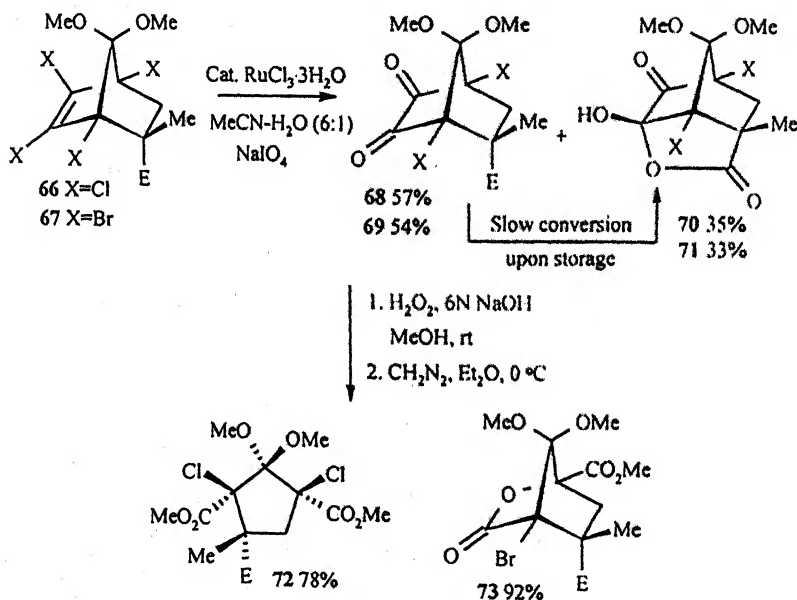
a) Cat.  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ ,  $\text{NaIO}_4$ ,  $\text{MeCN-H}_2\text{O}$  (6:1),  $0^\circ\text{C}$ , 1 h, 94%

b) 1)  $\text{H}_2\text{O}_2$ , 6N  $\text{NaOH}$ ,  $\text{MeOH}$ ,  $0-15^\circ\text{C}$ ; 2)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$ , 89%

When the 1,1-disubstituted olefinic adducts possess an interactive group such as an ester, as for example **66** and **67**, a mixture of diketones **68**, **69** and  $\alpha$ -keto hemiacetals **70**, **71** was

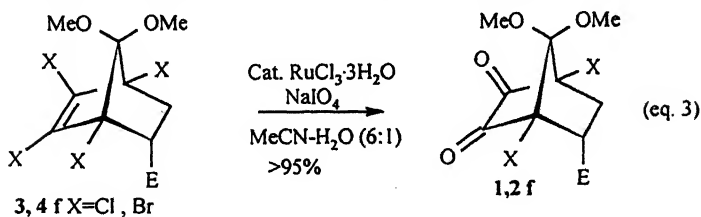
formed. Upon storage, the diketones were gradually converted to the  $\alpha$ -keto hemiacetals. A Diels-Alder reaction between tetrachloro-5,5-dimethoxycyclopentadiene **5** and methyl methacrylate gave the *endo* adduct **66** in high yield (Table 1A.1, page no. 204).<sup>27</sup> The tetrabromo derivative **67** was similarly prepared in almost quantitative yield by refluxing the tetrabromo-5,5-dimethoxycyclopentadiene **6** and methyl methacrylate under neat condition.

Scheme 19



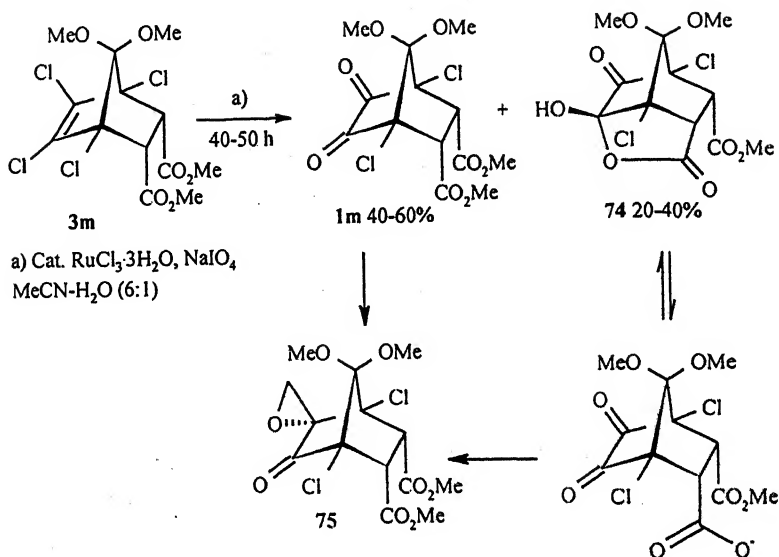
Interestingly, when there is no substituent on the ester bearing carbon, only the  $\alpha$ -diketone was obtained exclusively from the  $\text{RuCl}_3$  oxidation (eq. 3).<sup>1</sup> This implies that the *exo* substituent has

some bearing on the conformation and reactivity of the molecule facilitating the formation of the lactone easily.



On the other hand, the *endo* diester derivative **3m** does not undergo  $\alpha$ -keto hemiacetal formation with the same ease as the adducts **66,67** but prolonged reaction time for 40-50 h furnished some detectable amounts, 20-40% of the hemiacetal **74** depending on the reaction time (Scheme 20). When the  $\alpha$ -keto hemiacetal **74** was subjected to diazomethane mediated ring expansion at 0 °C to room temperature, the  $\alpha$ -ketospiroepoxide **75** was obtained in near quantitative yield. The spectral data and the melting point of the compound **75** formed, matches with the epoxide, previously obtained from our lab when the  $\alpha$ -diketone **1m** was treated with  $\text{CH}_2\text{N}_2$  for the purpose of ring expansion of the  $\alpha$ -diketone.<sup>28</sup> The  $\alpha$ -keto hemiacetal could exist in equilibrium with  $\alpha$ -diketone and the latter underwent a highly stereoselective epoxidation. The approach of the reagent to one of the carbonyl groups of the  $\alpha$ -diketone was exclusively from the *exo*-face giving the spiro epoxide where the oxygen occupies the *endo* position.

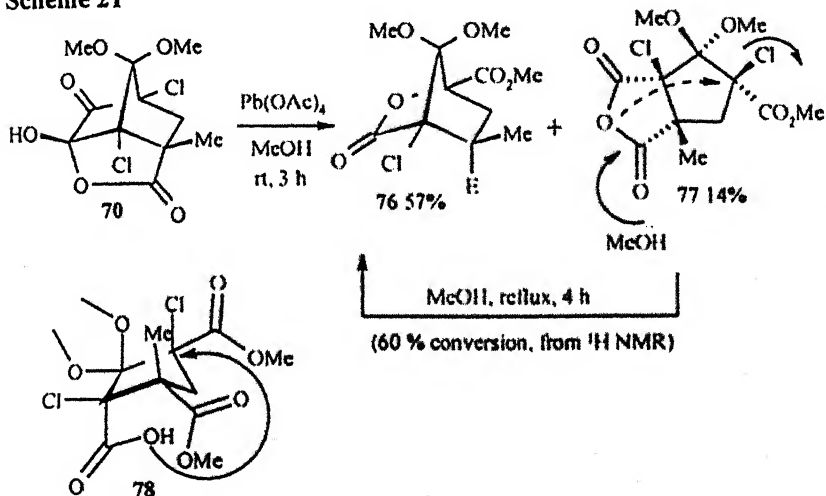
## Scheme 20



As anticipated the basic cleavage of the chloro  $\alpha$ -diketone **68** furnished the highly functionalized cyclopentane derivative **72**, having four contiguous quaternary centers. The bridged lactone **73** was exclusively acquired from the bromo diketone **69** (Scheme 19). Unexpectedly, the LTA cleavage of the hemiacetal **70** furnished the bridged lactone **76** in 57% of yield (Scheme 21). To unravel the mechanistic details for the formation of the unusual bridged lactone **76**, we looked at this reaction more carefully and noticed the formation of a minor compound, the expected anhydride **77** in 14% of yield. The carbonyl group of anhydride and ester appeared at 173.3 ppm in  $^{13}\text{C}$  NMR and the IR spectrum clearly showed anhydride stretchings at 1850 and 1780  $\text{cm}^{-1}$ , while ester carbonyl showed at

1720  $\text{cm}^{-1}$ . The anhydride **77** was isolated and treated with absolute MeOH under reflux condition to afford the bridged lactone **76** (slow conversion). This prompted us to explain the mechanism as shown in Scheme 21. The solvent MeOH opens up the anhydride in the reaction medium to give a reactive conformer **78** in which the axial COOH group is suitably disposed to trigger an intramolecular  $\text{S}_{\text{N}}2$  reaction at the quaternary  $\alpha$ -chloro ester center leading to the bridged lactone in excess.

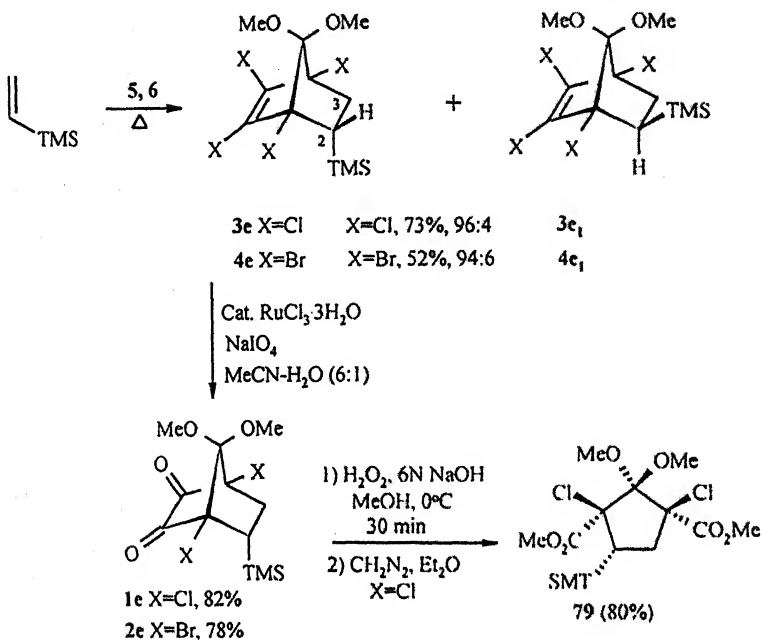
Scheme 21



Trimethylsilyl group is an important surrogate for hydroxyl functionality.<sup>29</sup> Incorporating the TMS group stereoselectively will provide an opportunity to carry out the synthesis wherein the hydroxyl group could be revealed at any convenient and desired stage. We incorporated the TMS group expediently using vinyl trimethylsilane as the dienophile (Scheme 22). The Diels-Alder reaction with tetrahalodimethoxy cyclopentadiene **5,6** with vinyl



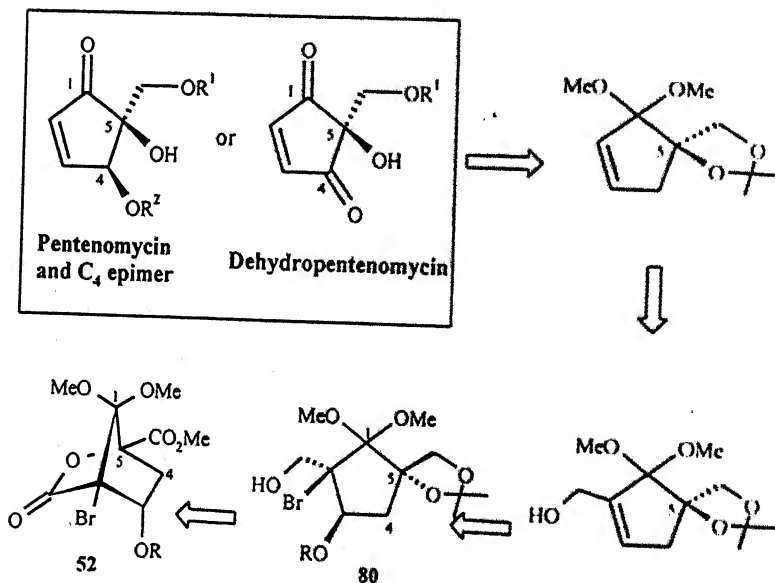
## Scheme 22: Diels-Alder reaction with vinyl trimethylsilane



trimethylsilane gave a mixture of *endo* and *exo* products **3,4 e, e<sub>1</sub>** with *endo* as the major product in each case. The major isomer was smoothly transformed to the corresponding diketones **1,2e** and further the cyclopentane derivative **79**, having TMS substituent was realized in 80% of yield, executing the same protocol. Here it is important to note that the trimethylsilyl group survives the H<sub>2</sub>O<sub>2</sub> condition, which is known to oxidize the TMS group.<sup>29</sup> The *exo* proton attached to the carbon bearing TMS group (C-2), is shielded in comparison to the *exo* proton attached to the C-3 carbon in <sup>1</sup>H NMR spectrum of adducts **3e** and **4e** (see spectral data from experimental section). The *exo* protons attached to C-2 appear at 1.95 and 1.93 ppm, while the *exo* protons attached to C-3 appear at 2.45

and 2.41 ppm respectively for **3e** and **4e**. Similar spectral pattern was observed for the diketones **1e**, **2e** and for the cyclopentane derivative **79** due to the presence of TMS group.

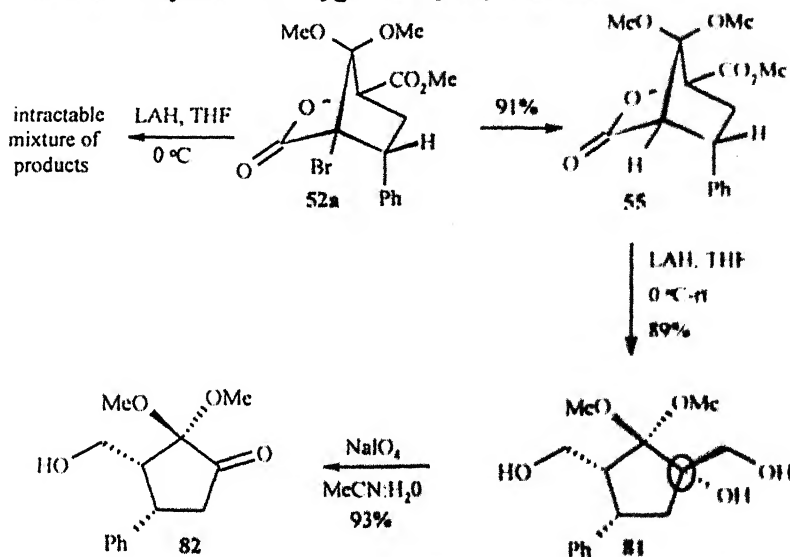
**2.2 Synthesis of pentenomycin analogues:** After successfully demonstrating the stereoselective formation of the potential bicyclic bridged lactones **51** and **52**, we planned to exploit the methodology for the construction of cyclopentane based natural products in a stereoselective manner. We particularly focused our attention towards the synthesis of pentenomycins. A brief literature is discussed in the introduction of this chapter. We envisioned a new strategy starting from the versatile bridged lactones **52**. The retrosynthetic analysis is depicted in Scheme 23. The key feature of our retrosynthetic analysis is to install the quaternary center C<sub>5</sub> present next to a carbonyl group in a stereoselective manner, which is also a structural feature in many naturally occurring molecules shown in Chart 3. A simple LAH reduction of the bicyclic lactone **52** would lead to the formation of oxygenated cyclopentane basic skeleton **80**, from which the synthesis of **14** could be achieved by conventional transformations. This reflects the simplicity and feasibility of our methodology, which is different from the already existing ones.

Scheme 23: Retrosynthetic analysis starting from the bicyclic lactone **52**

To check the feasibility of our plan we carried out the LAH reduction of the model substrate, the bridged lactone **52a**. We were not successful in isolating any product from the reaction mixture. The LAH reduction was then performed on the lactone **55**, derived from the bridgehead hydrodebromination of **52a** using  $\text{Bu}_3\text{SnH}$ . The polyhydroxylated cyclopentanoid derivative **81** was acquired in 89% of yield. The cyclopentanoid **81** has the required quaternary center present in pentenomycins and the carbocyclic nucleosides.<sup>17,24,25</sup> The 1,2-diol moiety of **81** was further cleaved using  $\text{NaIO}_4$  in 1:1 MeCN and water to give the ketone **82**, which could be used to incorporate amino functionality for the synthesis of amino cyclopentanoids and

further to create the enone part of the pentenomycins and related natural products.<sup>17, 30</sup>

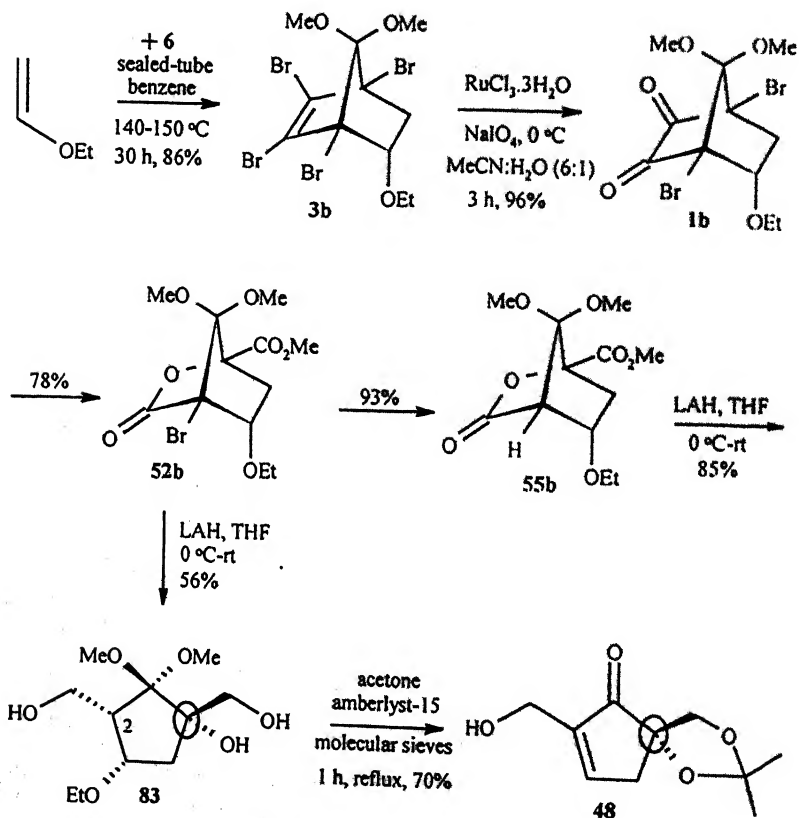
Scheme 24: Synthesis of oxygenated cyclopentanoids



For synthesis of pentenomycins, we started with ethyl vinyl ether adduct 3b. It was prepared in 85% yield from tetrabromo dimethoxycyclopentadiene and ethyl vinyl ether in benzene in a sealed-tube at 140-150 °C for 30 h. The Diels-Alder adducts prepared were given in a tabular form in experimental section. The adduct 3b was oxidized to the  $\alpha$ -diketone 1b in near quantitative yield (Scheme 25). As discussed earlier, the alkaline  $H_2O_2$  cleavage reaction of 1b furnished a single regioisomer of the bromo lactone 52b in 78% of yield (Scheme 13). The hydrodebromination of the bridged lactone 52b by radical reaction followed by LAH reduction

of **55b**, furnished the polyhydroxylated cyclopentanoid derivative **83**, with the required quaternary center of pentenomycins (Scheme 25).

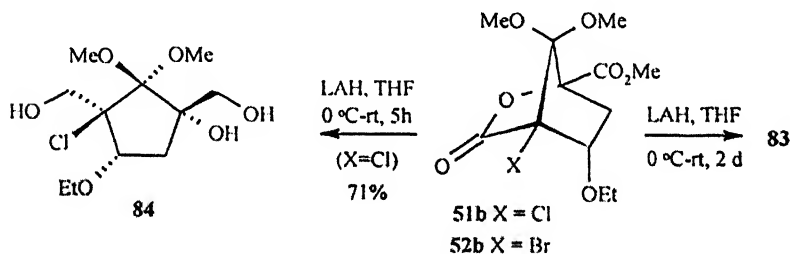
Scheme 25: Synthesis of 2-hydroxymethyl 4-deoxy pentenomycin derivative



Surprisingly, a direct LAH reduction of bromolactone **52b** in THF also furnished the same compound **83** in 56% of yield, although we anticipated inversion of stereochemistry at C-2. The formation of cyclopentanoid derivative **83** without an inversion at C-2 via both the pathways reveals that an electron-transfer radical mechanism is operative in the LAH reduction of the bromolactone **52b**.<sup>31</sup> We also

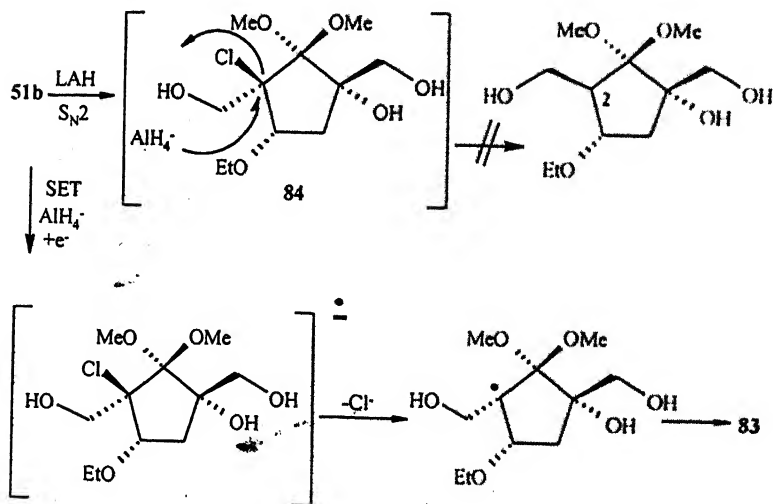
performed the LAH reduction of the corresponding chlorolactone **51b** to achieve the same compound **83**. By giving shorter reaction time at room temperature the intermediate cyclopentanoid **84** having  $\alpha$ -chloro hydroxymethyl group was obtained, however by continuing the reaction for 2 days, the compound **83** was obtained (Scheme 26). This demonstrates a short synthetic route to the polyhydroxylated cyclopentanoid **83**, the advanced intermediate to pentenomycin and a crucial intermediate in the synthesis of carbocyclic nucleosides.<sup>24,25</sup>

**Scheme 26:** LAH reduction of bridged lactones



A plausible mechanism for the LAH reduction of **51b** is depicted in Scheme 27. The  $\text{S}_{\text{N}}^2$  reaction at the sterically hindered C-2 carbon is apparently not feasible. The formation of **83** can be explained on the basis of a SET pathway involving an electron transfer from LAH to **51b** (or **52b**) to generate the radical anion of **51b** (or **52b**). On losing  $\text{Cl}^-$  (or  $\text{Br}^-$ ), this radical anion would produce a radical which then abstracts a hydrogen atom to give **83**. At this stage it is not clear as to why hydrogen abstraction is taking place only from one face to give a single product. Further experiments to probe the mechanistic details are underway in our group.

Scheme 27: Evidence for SET Mechanism in LAH reduction

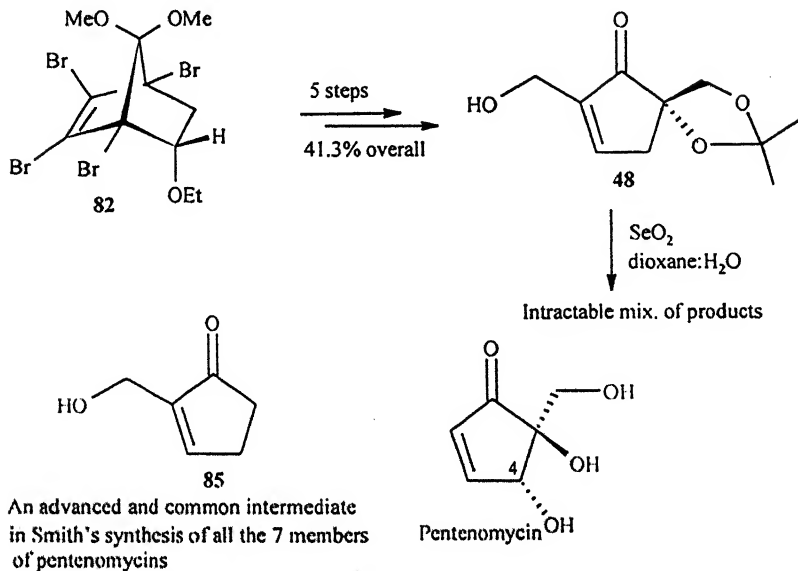


The enone moiety of pentenomycin was simply achieved by using acetone in amberlyst-15. The substrate **83** affords 2-hydroxymethyl 4-deoxy pentenomycin derivative **48** in 70% of yield. All the three desired reactions, namely the protection of the diol as acetonide, the deprotection of the dimethyl acetal and finally the elimination of the ethoxy substituent taking place in a single pot, which rarely happens in a synthetic sequence.

We could able to accomplish a very short and stereoselective sequence for the synthesis of 2-hydroxymethyl-4-deoxy pentenomycin derivative **48** in 5 steps in an overall yield of 41.3% starting from the tetrabromonorbornyl derivative **3b** (Scheme 28). The overall yield is calculated from the synthetic sequence shown in Scheme 25. Leaving apart the quaternary center of **48**, the

cyclopentanoid **85** is a common intermediate in Smith's synthesis of all the seven members of pentenomycins.

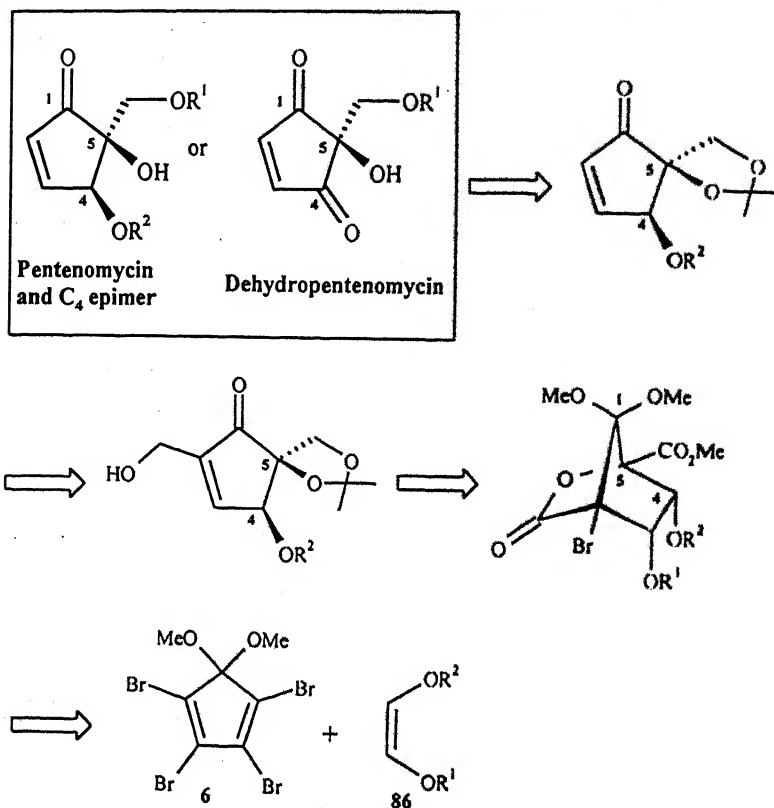
**Scheme 28**



At this stage we wanted to install the hydroxyl group at C-4, the required feature of the pentenomycin structure. The preliminary attempts using SeO<sub>2</sub> for the purpose lead to an intractable mixture of products (Scheme 28). In order to circumvent the difficulties encountered in SeO<sub>2</sub> reaction, we wanted to incorporate the hydroxyl group at an early stage by choosing suitable dienophiles of type **86**, which could provide oxygen at the fourth position, as presented in the retrosynthetic analysis (Scheme 29). The key feature of the retrosynthesis shown in scheme 29 is to establish the C-5 quaternary center as well C-4 stereocenter at an early stage in a stereoselective manner.



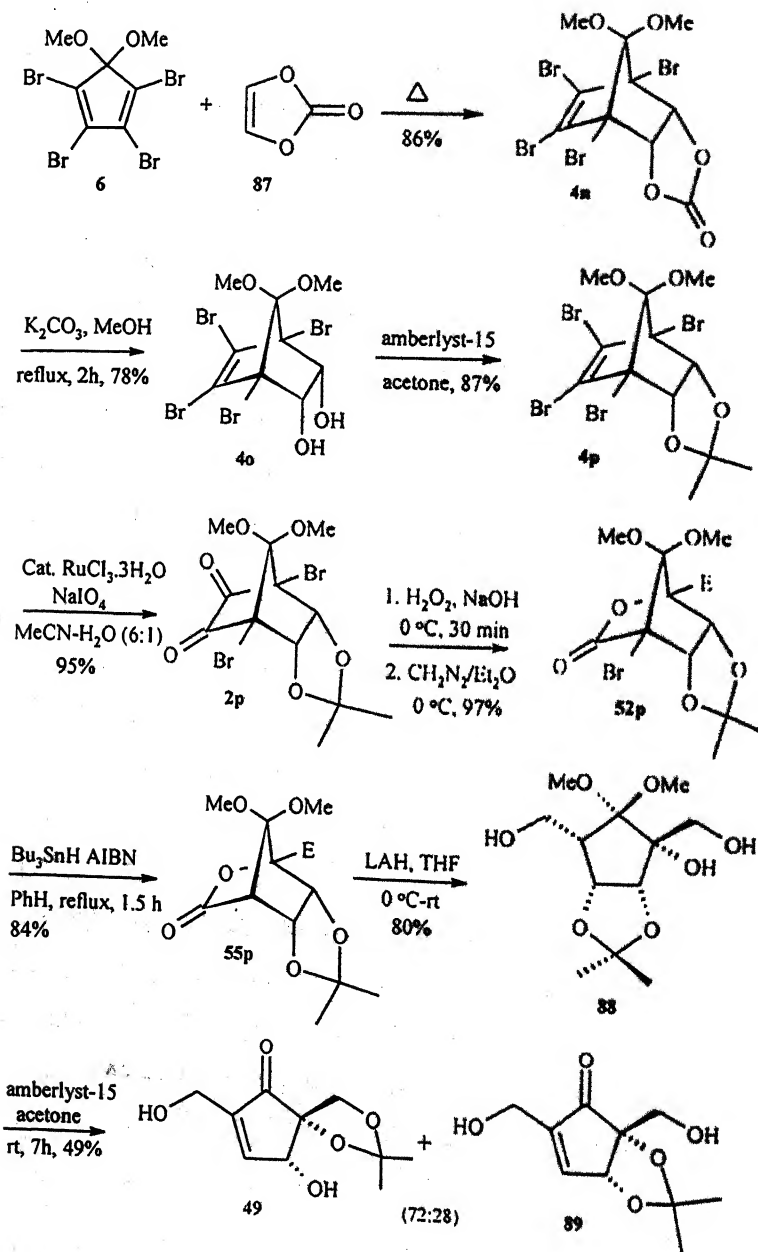
Scheme 29: Retrosynthetic analysis starting from the bicyclic lactone



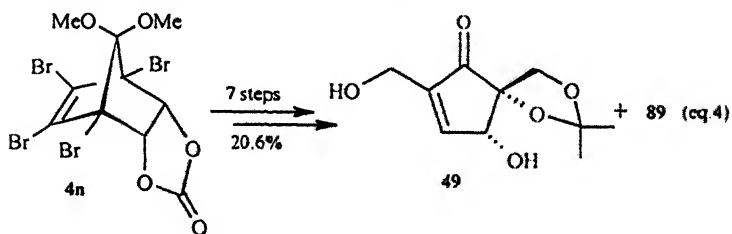
The vinylene carbonate **87** was used as the dienophile of choice for carrying out the synthesis (Scheme 30). A Diels-Alder reaction between tetrabromodimethoxy cyclopentadiene **6** and vinylene carbonate **87** furnished the *endo* adduct **4n** in 86% of yield. Since the carbonate is sensitive for subsequent steps, it was deprotected to diol **4o** and then reprotected as acetonide **4p**. Then we performed the same sequence of reactions as depicted in Scheme 25.

The acetonide **4p** was oxidized to yellow crystalline diketone **2p** in near quantitative yield, which was further cleaved to furnish the bromolactone **52p** in 97% yield. It is important to note that although we characterized all the intermediates thoroughly in the sequence, but the reaction up to the bridged lactone stage **52p** starting from the tetrabromo adduct **4n**, could now be carried out without any column purification. The crude reaction mixture was pure enough to be used directly for the next step, which is highly gratifying in a multi-step synthesis. The reductive hydrodebromination of **52p** followed by LAH reduction of the reduced lactone **55p** affords the polyhydroxylated cyclopentanoid derivative **88** (Scheme 30). The highly oxygenated cyclopentanoid **88** is a useful template that can be widely employed in the synthesis of highly functionalized five-membered rings, for example, carbocyclic nucleosides (Chart 3). The required quaternary center was acquired in a stereoselective manner and this advance intermediate contains all the required features of pentenomycin at C-1, C-4 and C-5. Once again subjecting the cyclopentanoid to amberlyst-15 in acetone furnished the products **49** and **89**, derived from four reactions taking place in a single pot, namely; i) the protection of diol, ii) the deprotection of acetonide, iii) the deprotection of acetal, and finally iv) the elimination of hydroxy functionality leading to the formation of 2-hydroxymethyl pentenomycin derivatives **49** and **89** in a ratio of 72:28 in 49% of yield (Scheme 30).

## Scheme30: Synthesis of 2-hydroxymethyl pentenomycin derivatives



The synthesis of 2-hydroxymethyl pentenomycin derivatives **49** and **89** was achieved by following a stereoselective sequence involving seven steps in an overall yield of 20.6% starting from the tetrabromonorbornyl derivative **4n** (eq. 4).



### 3. Conclusion

In short, we have accomplished a new synthesis of 2-hydroxymethyl 4-deoxy-pentenomycin derivative **48**, and functionalized pentenomycin derivatives **49** and **89** utilizing easily accessible starting materials, applying a simple and novel methodology recently developed in our laboratory. Further, the methodology used could be developed as a new and general synthesis of cyclopentenones. The advanced intermediates **48**, **49**, **88** and **89** are also of considerable importance as glycosidase inhibitors and carbocyclic nucleosides.<sup>24,25</sup>

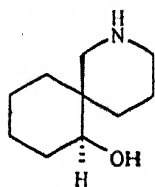
## Chapter 1B

### A Novel Radical Approach to Unusual Spiro-Lactam Building Blocks

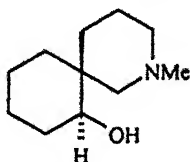
#### 1. Introduction

The development of synthetic sequences aimed at achieving desired molecular complexity present in multi-stereocentered polycyclic targets employing simple and easily accessible starting materials in a rapid, proficient as well as stereoselective manner continues to be a major challenge in contemporary organic synthesis. In this context, this chapter describes a novel, remarkably efficient, and serendipitously discovered synthesis of functionalized spirocyclic lactams via radical mediated intermolecular C-C bond formation. The azaspirocyclic substructures occur in numerous biologically active

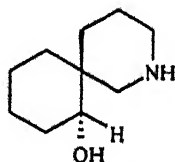
**Chart 4:** Structure of some naturally occurring azaspirocycles



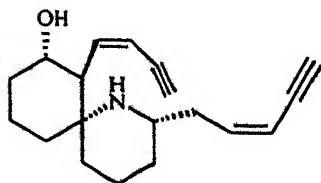
**nitramine**



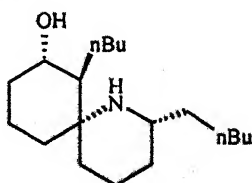
**sibirine**



**isonitramine**



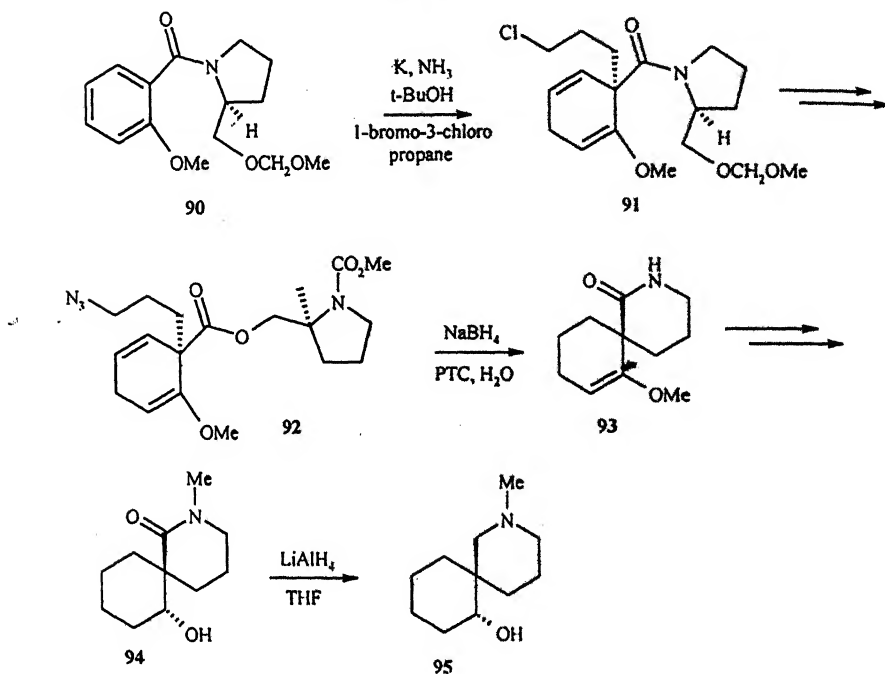
**histrionicotoxin 1**



**perhydrohistrionicotoxin 2**

alkaloids such as histrionicotoxin,<sup>32</sup> sibirine,<sup>33</sup> nitramine,<sup>34</sup> isonitramine,<sup>34</sup> fascicularin<sup>35</sup> etc. Some of these are shown in Chart 4.

**Scheme 31:** Synthesis of (+)-sibirine

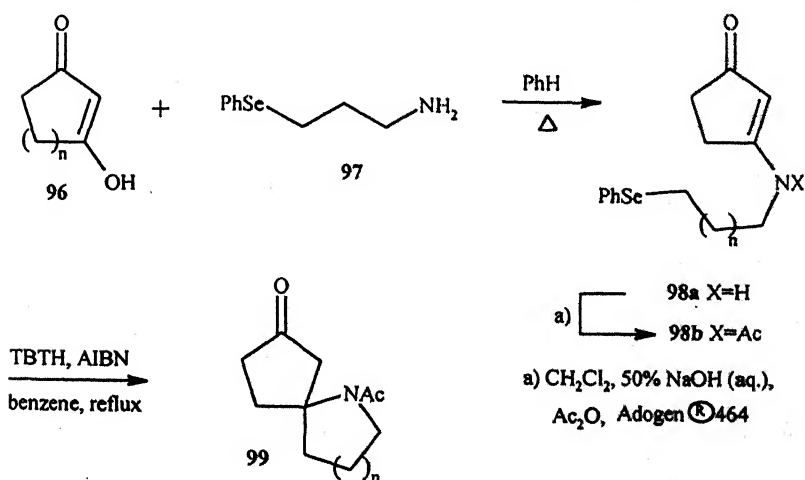


The spiro lactams also function as the crucial building blocks for the synthesis of 2-azaspiro[5,5]undecane group of alkaloids (Scheme 31).<sup>34</sup> Shultz reported efficient enantioselective synthesis of 2-azaspiro[5,5]undecane group of alkaloids such as sibirine, nitramine and isonitramine involving the stereoselective Birch reductive alkylation strategy. The synthesis of sibirine started with stereoselective Birch reductive alkylation of anisic acid derivative **90** with 1-bromo-3-chloropropane to furnish **91**, using a chiral auxiliary, L-prolinol. The

intermediate **91** was further transformed to the azide **92**, the sodium borohydride reduction under phase transfer condition gave the spirocyclic lactam **93**. Finally, the LAH reduction of hydroxy lactam **94** furnished the (+)- sibirine **95** (Scheme 31).

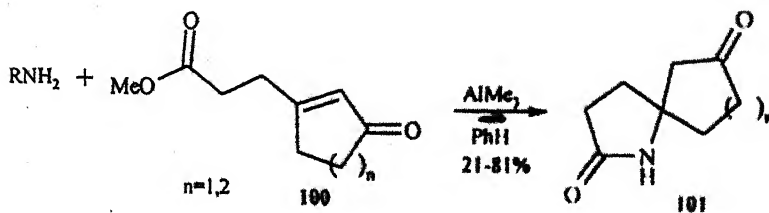
There are few methodologies that are known in the literature for the construction of azaspirocyclic ring systems.<sup>35-37</sup> Simpkins reported the synthesis of azaspirocyclic ketones **99** using a radical cyclization (Scheme 32).<sup>36</sup> The condensation of cyclic diones **96** with amines **97** furnished the vinylogous amides **98a**, which was acetylated by subjecting to a two phase system,  $\text{CH}_2\text{Cl}_2$ -50% aq. NaOH in acetic anhydride using Adogen® 464 as phase-transfer catalyst. The resulting acetylated compounds **98b** underwent cyclization, using TBTH, AIBN in benzene under reflux condition to give the spirocyclic products **99** (Scheme 32).<sup>36</sup>

**Scheme 32:** Radical cyclization route to aza spiro compounds



Two more recent examples are presented below. Tietze reported an efficient synthesis of spirocyclic lactams **101** from primary amines, cycloenones containing propionate side chain **100** involving a two-component domino process that includes the formation of a carboxylic amide followed by a Michael addition in the presence of trimethylaluminium (Scheme 33).<sup>37a</sup>

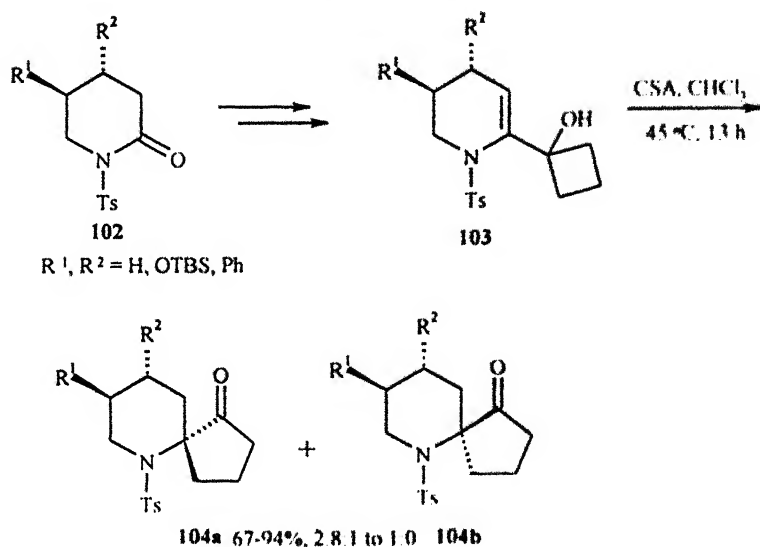
Scheme 33: Domino spirocyclization by Tietze



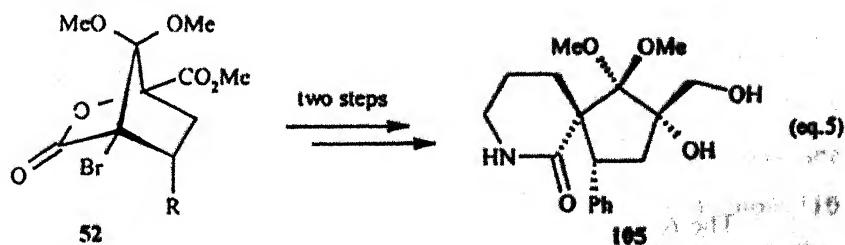
Recently, Dake reported a semi-pinacol type ring expansion of cyclobutanols of type **103** to provide azaspirocyclic ketones **104a,b** by the action of camphorsulfonic acid in high yield and good stereoselectivity (Scheme 34).<sup>37b</sup> The yields in this rearrangement are high (67-94%) and a diastereomeric ratio of 2.8:1 to 1:0 of **104a,b** was observed. The cyclobutanols **103** were prepared from *N-p*-toluenesulfonyl lactams **102**.



Scheme 34: Semipinacol-Type ring expansion of cyclobutanols



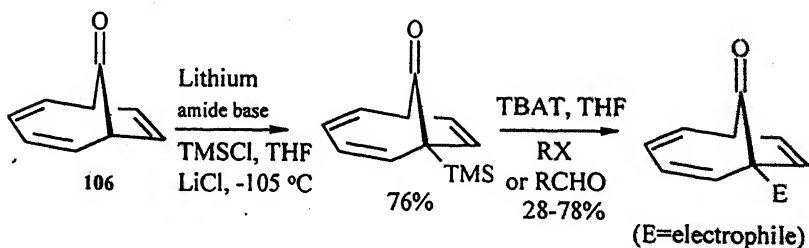
In this section, development of a new synthesis of novel spiro-lactam building blocks **105** via a radical mediated, intermolecular bridgehead C-C bond formation of the versatile bridged lactones **52** with acrylonitrile followed by LAH reduction of the adduct, is described (eq.5).



## 2. Results and Discussion

The anti-Bredt nature of bridgehead enolates derived from ketones having small bridges is expected to make their generation difficult or impossible.<sup>38</sup> However it is possible to generate carbanion at bridgehead in certain cases, but the intermediate anion appears to be highly reactive and displays chemistry that is difficult to control. For the ketone **106**, 'external quench protocols' were ineffective in trapping the carbanion, leading only to undesired dimeric aldol product. Deprotonation under insitu quench conditions in the presence of TMSCl at  $-105\text{ }^{\circ}\text{C}$  gave the required product.<sup>39</sup> The insitu quench approach is incompatible with carbon-centered electrophiles such as MeI; allyl bromide, benzaldehyde, etc. However, indirect method involving fluoride mediated silyl exchange was successful (Scheme 35).

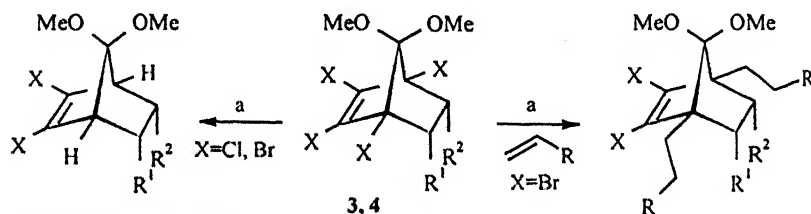
Scheme 35



The reluctance of carbanions derived from norbornanones and related systems to undergo reaction with carbon-centered electrophiles at the bridgehead position<sup>38</sup> prompted us to explore radical mediated C-C bond formation employing their generically intimate and often

inevitable precursors, viz, tetrahaloronorbornenes.<sup>4</sup> We successfully achieved the selective reduction of bridgehead halogens, and the C-C bond formation at the bridgehead using preparatively simple protocol employing tributyltin hydride leaving vinylic halogens intact (Scheme 36).<sup>8</sup> It is noteworthy that attempts to make a C-C bond at the bridgehead of 7-norbornane derivatives employing strong base which can deprotonate the bridgehead proton were not successful.<sup>38</sup> In this perspective, our results were highly encouraging.

**Scheme 36:** Bridgehead C-C bond formation and hydrodehalogenation<sup>7</sup>

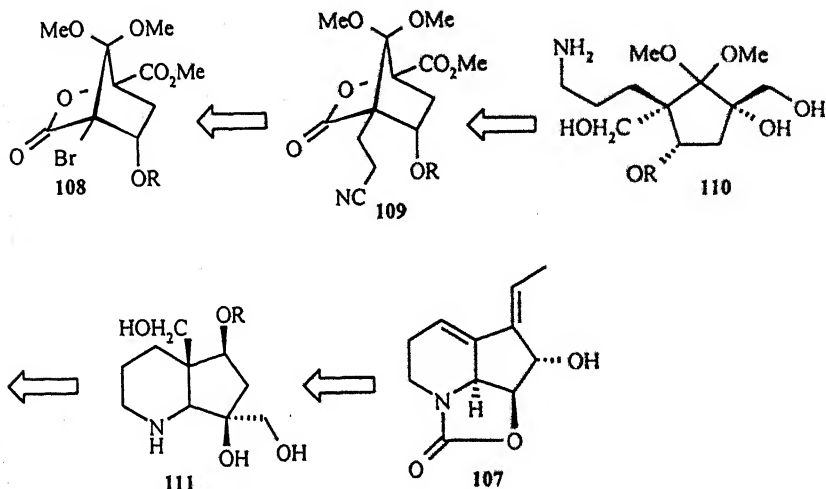


a)  $\text{Bu}_3\text{SnH}$ , AIBN, PhH, reflux

In connection with an ongoing project towards the synthesis of antibiotic streptazolin **107**,<sup>40</sup> we envisioned a useful new sequence for stereocontrolled formation of the unusual hexahydropyridine ring system **111** as diagrammed in retrosynthetic analysis (Scheme 37). The bridgehead C-C bond formation of the bicyclic lactone **108** followed by LAH reduction of the adduct **109** would reveal the cyclopentane derivative **110**, having amino alkyl side chain. The cyclopentanoid **110** could serve as a potential precursor for the desired hexahydropyridine derivative **111**. Contrary to our expectation, the LAH reduction of the

acrylonitrile addition product **109** directly lead to the spiro amide **105** (Scheme 39).

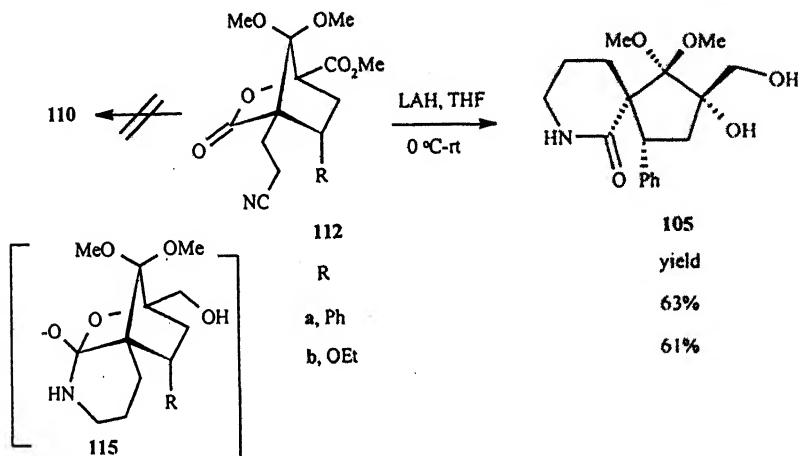
**Scheme 37:** Retrosynthetic analysis starting from bridged lactone



In the previous section, we have discussed the preparation of the bridged bicyclic lactones **52** from the corresponding  $\alpha$ -diketones (Scheme 13) in an efficient and highly regioselective manner, which were further utilized in the synthesis of polyhydroxylated cyclopentanoids. The bicyclic bromolactones **52** were proved to be the promising substrates for the radical mediated intermolecular C-C bond formation at the bridgehead. The results are depicted in Scheme 38. A slow addition of a benzene solution of TBTH to a refluxing mixture of **52a** and acrylonitrile as the radicophile resulted in the formation of 75% of the bridgehead-functionalized product **112a** along with 7% of the reduced lactone **55a**. By employing photochemical conditions,

**113** was obtained in 33% of yield along with 40% of the hydrodebromination product **114** (eq. 6). The steric factor appears to be responsible for the diminished yield of adduct **113**.

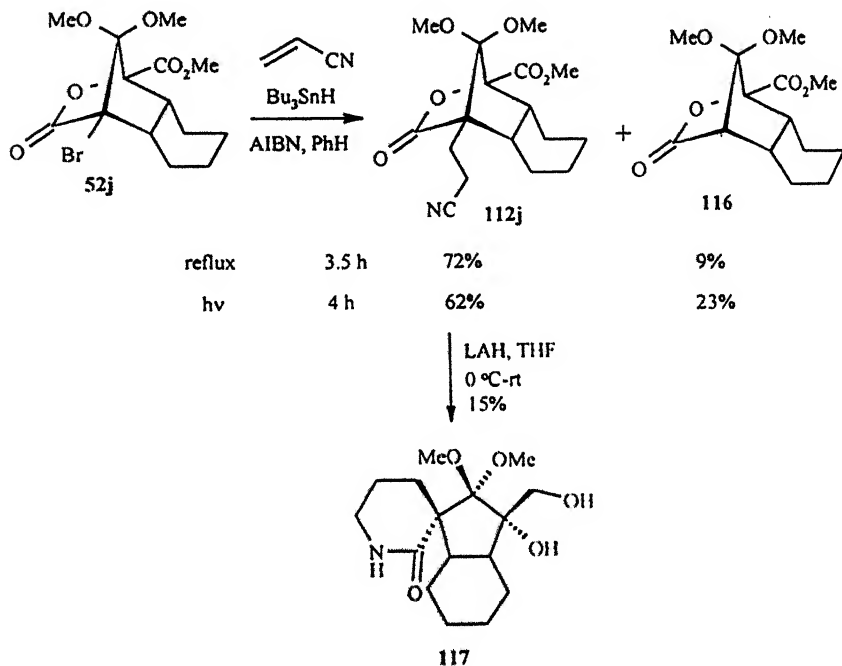
**Scheme 39: Synthesis of spirocyclic lactams**



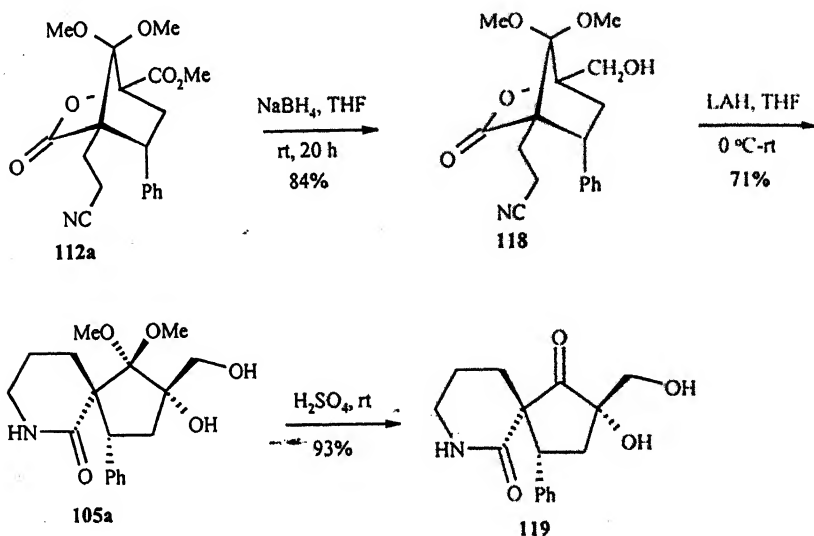
After successfully accomplishing the synthesis of functionalized lactones **112** in good yield, we wanted to check the feasibility of our plan shown in Scheme 37. The LAH reduction of **112a** was carried out. In contrast to our anticipation, a 7-azaspiro[4.5]decan-6-one **105a** was obtained in 63% yield (Scheme 39), instead of the functionalized cyclopentanoid derivative **110**. The lactam carbonyl group appeared at 174.7 ppm in  $^{13}\text{C}$  NMR spectrum. The lactam carbonyl group did not undergo further reduction with LAH in the reaction mixture even when it was refluxed with excess reagent in THF for several hours. This is probably because of the firm

engagement of the lactam carbonyl under the reaction conditions as shown in 115.

**Scheme 40 : Synthesis of tricyclic spirolactam**



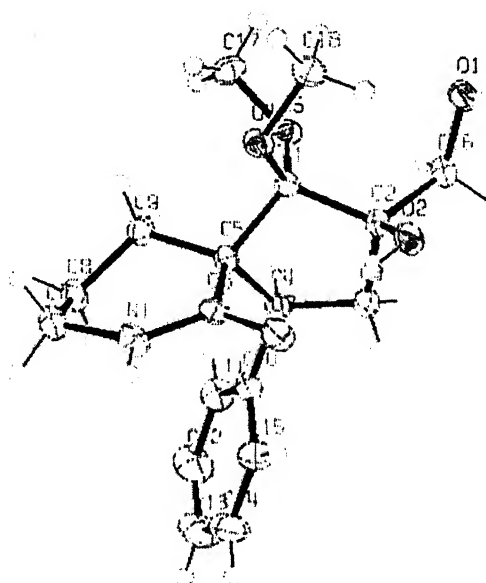
The tricyclic lactone **52j** also gave excellent yield of the bridgehead functionalized product **112j**, when subjected to TBTH under reflux as well photochemical conditions along with 9-23% of the reduced lactone **116** (Scheme 40). The functionalized product **112j** was treated with LAH to furnish the tricyclic spirolactam **117**, albeit in low yield (15%). The product **117** has a combination of fused and spiro elements on a five membered ring.

**Scheme 41:** Sodium borohydride reduction of bridghead ester

We thought that pre-reducing the lactone moiety in **112a** chemoselectively to obtain the corresponding lactol and then carrying out the LAH reaction would probably change the reaction course. We employed  $\text{NaBH}_4$  for the purpose. However the reduction of **112a** with  $\text{NaBH}_4$  in THF at room temperature furnished the alcohol **118** (Scheme 41). The methyl ester was reduced in preference to cyclic ester ( $\gamma$ -lactone) which is not commonly observed except for few scattered reports of reduction of ester bearing an  $\alpha$ -electron withdrawing group.<sup>41</sup> Our result illustrates a new example of  $\text{NaBH}_4$  reduction of carboxylic esters bearing an  $\alpha$ -oxygen substituent. Apparently chelation and/or inductive activation accelerate the reaction. The spiroamide **105a** was realized by treatment of the alcohol **118** with LAH. The acidic

hydrolysis of the compound **105a** afforded the azaspirocyclic ketone **119**. A single crystal X-ray analysis was carried out to prove the structure and relative stereochemistry of the aza spirocycle **105a** unequivocally (Figure 1). The ortep diagram of **105a** is shown in Figure1.

**Figure 1:** Ortep structure of the 7-azaspiro[4.5]decan-6-one **105a**



### 3. Conclusion

In summary, we have developed a new sequence of reaction in which bridgehead C-C bond formation of the potential bridged bicyclic lactones provides a short and efficient route to extract novel, unexplored structural motifs, viz, 7-azaspiro[4.5]decan-6-ones from



norbornyl derivatives. We are further interested in studies of the biological activity of the lactams and construction of azaspirocyclic alkaloids, utilizing the methodology described.

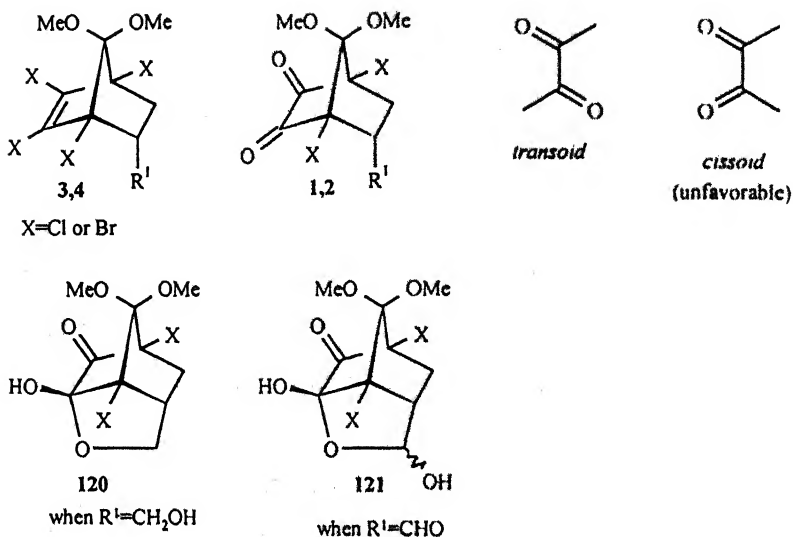
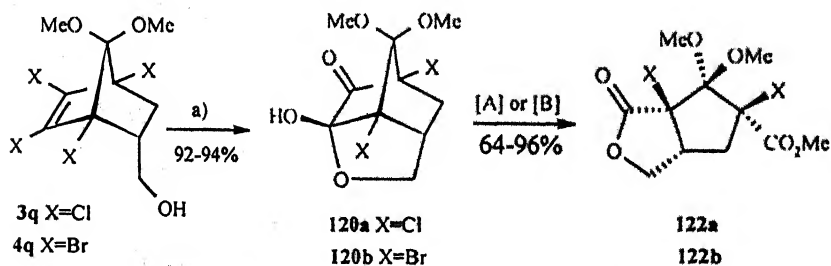
## Chapter 1C

### A short synthetic route to $\gamma$ - and $\delta$ -cyclopentannulated lactones

#### 1. Introduction

The  $\alpha$ -diketones are versatile and reactive intermediates. One of the obvious consequences of the geometrical constraints on the  $\alpha$ -dione moiety in norbornyl derivatives **1,2** is the imposition of the unfavorable cisoidal conformation, rendering one of the carbonyl groups of the  $\alpha$ -dione to acquire high propensity to interact either with a nucleophilic or electrophilic substituent, which is suitably disposed, in order to avoid unfavorable electrostatic interactions.<sup>1,12</sup> Thus, when the *endo*-substituent  $R^1$  in **3,4** is hydroxymethyl, a stable hemiacetal **120** (Scheme 42) in which one of the carbonyl groups of  $\alpha$ -dione is switched to  $sp^3$ -hybridized carbon was isolated under the same catalytic  $RuCl_3 \cdot 3H_2O$  oxidation condition as depicted in Scheme 1. On the other hand, an electrophilic *endo*-substituent ( $R^1=CHO$ ) promotes the formation of a stable hydrate **121** (Figure 2).<sup>1</sup> We describe in this section a novel, short and efficient methodology to realize the cyclopentannulated  $\gamma$ -lactones making use of the persuasive advantages of the structural flexibility and stereochemical control offered by the tetrahalonorbornene derivatives.

Figure 2

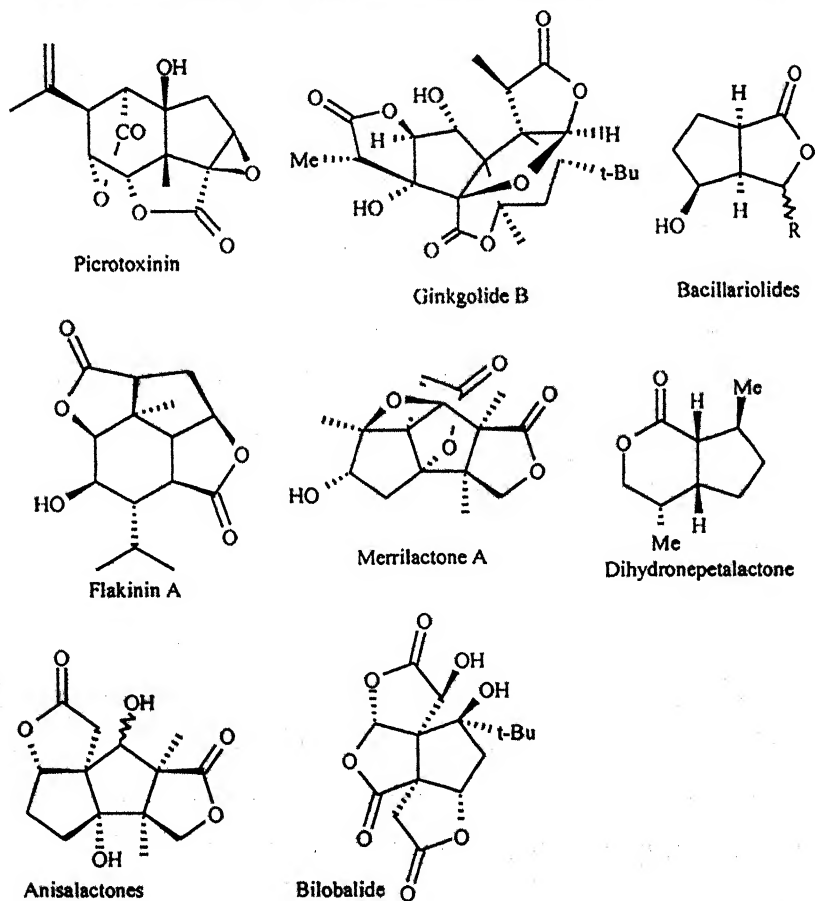
Scheme 42: Cyclopentannulated  $\gamma$ -lactones

a)  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ ,  $\text{NaIO}_4$ ,  $\text{MeCN:H}_2\text{O}$  (6:1), 2-6 h, [A] =  $\text{Pb}(\text{OAc})_4/\text{MeOH:PhH}$  (1:2), rt  
[B] = (i)  $\text{H}_2\text{O}_2/\text{NaOH}$ ,  $\text{MeOH}$ , rt, (ii)  $\text{CH}_2\text{N}_2/\text{Et}_2\text{O}$ , 0 °C

During our preliminary investigations on the chemistry and reactivity of hemiacetals 120, we successfully demonstrated an efficient synthesis of  $\gamma$ -lactone-fused cyclopentanoids 122 employing both

neutral using  $\text{Pb}(\text{OAc})_4$  (method A), and basic using alkaline hydrogen peroxide (method B), cleavage reaction conditions (Scheme 42). We were delighted to find that the  $\gamma$ ,  $\delta$ -Lactone-fused cyclopentanoids are among the most abundant substructures found in numerous naturally occurring molecules. A cyclopentane ring *cis*-fused at the  $\alpha,\beta$ -bond of the  $\gamma$ ,  $\delta$ -lactone is the basic structural unit of many complex and

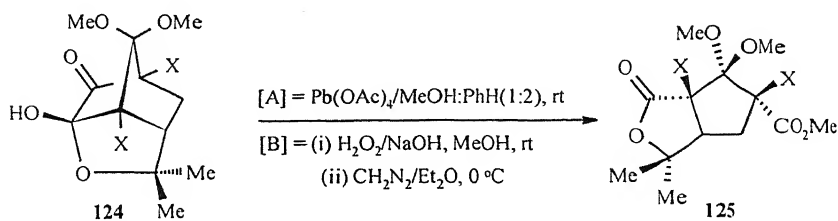
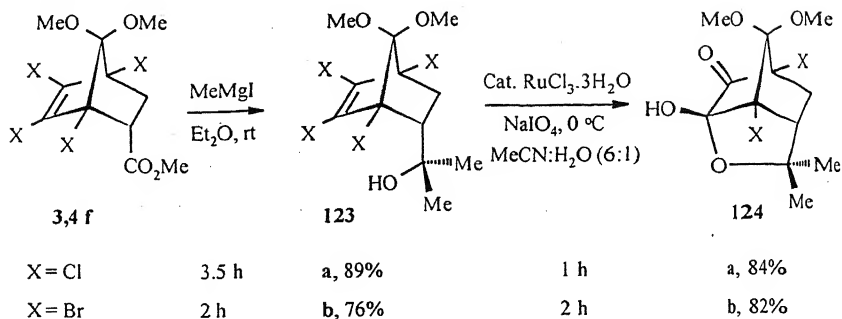
**Chart 5:** Natural products containing cyclopentannulated  $\gamma,\delta$ -lactones as substructure



challenging natural products like Picrotoxinin, Bacillariolides, Anisalactones, Merrilactone A, Bilobalide, Ginkgolide, Flakinin, Dihydronepatalactone etc.<sup>42</sup> Few representative examples are shown in Chart 5.<sup>42</sup> The cyclopentannulated  $\gamma$ -,  $\delta$ -lactones are not only responsible for the biological activity, but also function as the basic building blocks for the synthesis of a variety of cyclopentanoid natural products (e.g., methylenomycin A and epimethylenomycin A).<sup>17c,30,43</sup> This provided us the impetus to conceive a convenient and general method for their preparation. Various synthetic methods have been adopted in the literature to acquire this important ring system,<sup>44</sup> however many of these are target oriented.

## 2. Results and Discussion

**2.1 Synthesis of  $\gamma$ -lactones:** To expand the scope of the process to obtain  $\gamma$ -lactone derivatives having substituents both in the lactone part as well as cyclopentane ring, tertiary alcohols **123** were identified as the suitable precursors. The alcohols **123** could, in principle, be prepared via the Diels-Alder reaction of tetrahalo-5,5-dimethoxycyclopentadiene **5,6** with either suitably substituted allyl alcohols or substituted methyl acrylate followed by the conversion of ester group to tertiary alcohol. The latter option was preferred because while substituted allyl alcohols are poor dienophiles, substituted methyl acrylate, on the other hand, provides higher reactivity, *endo*-selectivity and flexibility of incorporating any desired pair of substituents on the tertiary carbon.<sup>12</sup>

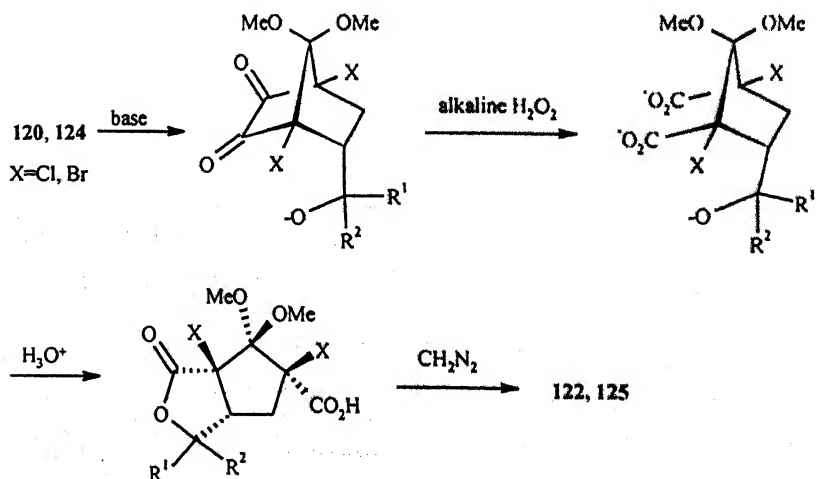
Scheme 43: Synthesis of  $\gamma$ -lactones

Substrate	Method	Time (h)	Yield (%) of 125	Overall yield from 3,4 f (%)
X=Cl	A	2	81	61
	B	1	86	64
X=Br	A	4	79	49
	B	1	81	51

Thus, the Diels-Alder adducts of methyl acrylate **3,4 f** obtained from corresponding tetrahalo-5,5-dimethoxycyclopentadiene **5,6** were smoothly transformed into the tertiary alcohols **123a,b** using Grignard reaction (Scheme 43).<sup>12</sup> Oxidation of these substrates with cat.  $\text{RuCl}_3$  and  $\text{NaIO}_4$  afforded the  $\alpha$ -keto hemiacetals **124a,b** in good to high yields. The  $\alpha$ -keto hemiacetals **124a,b** were subjected to both  $\text{Pb}(\text{OAc})_4$

and alkaline  $\text{H}_2\text{O}_2$  mediated cleavage reaction to give highly substituted  $\gamma$ -lactone-fused cyclopentanoids **125a,b** in good overall yield from the Diels-Alder precursors **3,4 f** (Scheme 43).<sup>12</sup>

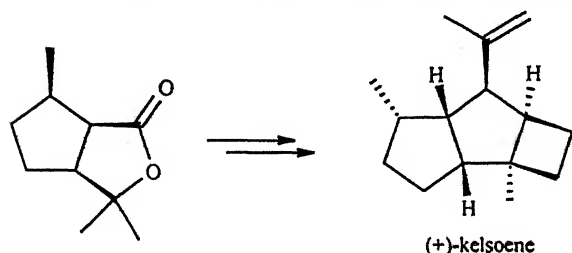
The tricyclic  $\alpha$ -keto hemiacetals **120** and **124** are important not only because of the occurrence of closely related substructure in some of the biologically active natural products<sup>45</sup> but also could serve as potential building blocks in organic syntheses. The method A directly furnished lactones **122** and **125** possessing methyl ester since MeOH was used as a cosolvent. In method B, which involves basic reaction conditions, the  $\alpha$ -keto hemiacetal could exist in equilibrium with  $\alpha$ -diketone and the latter underwent cleavage with alkaline hydrogen peroxide to give the diacid first. Upon acidic work up, one of the carboxylic acid group lactonized with the free primary alcohol and the



other carboxylic acid group was converted to methyl ester by treatment with diazomethane (Scheme 44).

There is a recent report,<sup>46</sup> in which such type of  $\gamma$ -lactones served as crucial building blocks for naturally occurring *cis:anti:cis* tricyclic sesquiterpene (+)-kelsoene (Scheme 45).

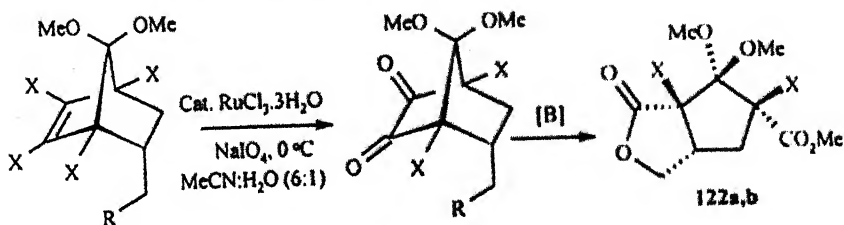
**Scheme 45:**  $\gamma$ -lactone-fused cyclopentanoid as the basic building block



It is interesting to note that the diketones bearing *endo* halomethyl groups **1,2g** and **1h** derived from the corresponding adducts **3,4 g** and **3h** also furnished, upon cleavage with alkaline  $\text{H}_2\text{O}_2$ , the  $\gamma$ -lactone derivatives **122a,b** in high yields (Scheme 46). The substrates **1,2g** and **1h** serve as potential precursors for the synthesis of the lactones **122a,b**, thus providing a choice from a range of allylic dienophile precursors, which contribute three carbons to the  $\gamma$ -lactone-fused cyclopentanoid skeleton.



Scheme 46: Diketones bearing halomethyl groups as precursors



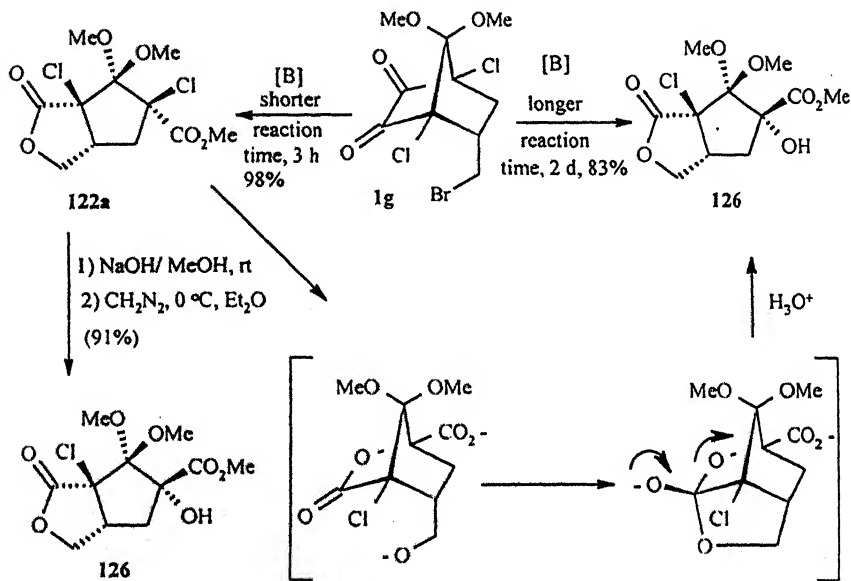
3g X=Cl, R=Br	15 min	1g, 89%	3h	122a, 98%
4g X=Br, R=Br	25 min	2g, 80%	30 min	122b, 95%
3h X=Cl, R=Cl	10 min	1h, 90%	3h	122a, 73%

[B] = (i)  $\text{H}_2\text{O}_2/\text{NaOH}$ ,  $\text{MeOH}$ , rt, (ii)  $\text{CH}_2\text{N}_2/\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$

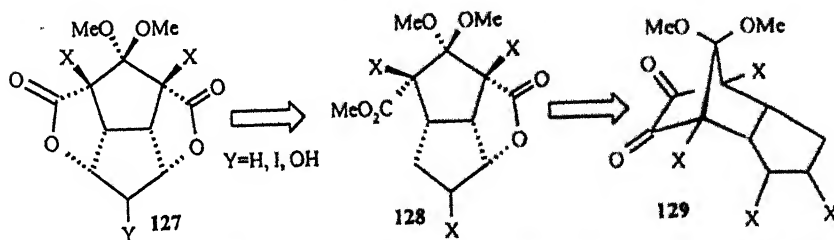
Subjecting the  $\alpha$ -dione **1g** with alkaline  $\text{H}_2\text{O}_2$  for three hours followed by diazomethane treatment furnished the  $\gamma$ -lactone-fused cyclopentane derivative **122a** (Scheme 46). However conducting the reaction for longer time (2 days), a one-pot, highly regio- and stereoselective transformation leading to  $\alpha$ -hydroxy ester bearing  $\gamma$ -lactone derivative **126** was observed. This is probably via the bridged-lactone intermediate as depicted in Scheme 47. The  $\alpha$ -hydroxy esters are important in organic syntheses; an  $\alpha$ -halo ester could serve as a precursor for the former through nucleophilic displacement of halide by hydroxide anion. But the halogens in  $\gamma$ -lactone derivative are tertiary in nature, and a  $\text{S}_\text{N}2$  reaction at this center would be rather difficult. However the  $\alpha$ -hydroxy ester **126** was realized through a lactone assisted, highly regio- and stereoselective strategy as shown in Scheme 47. To chemically confirm, the lactone **122a** was further treated with

NaOH to afford the  $\alpha$ -hydroxy ester derivative **126**, which supports our proposal (Scheme 47).

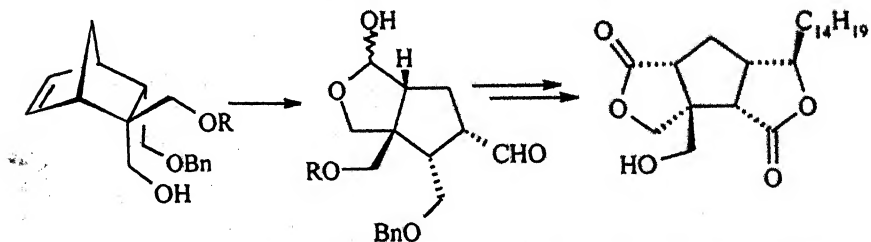
**Scheme 47:** Regio- and stereoselective conversion to  $\alpha$ -hydroxy ester



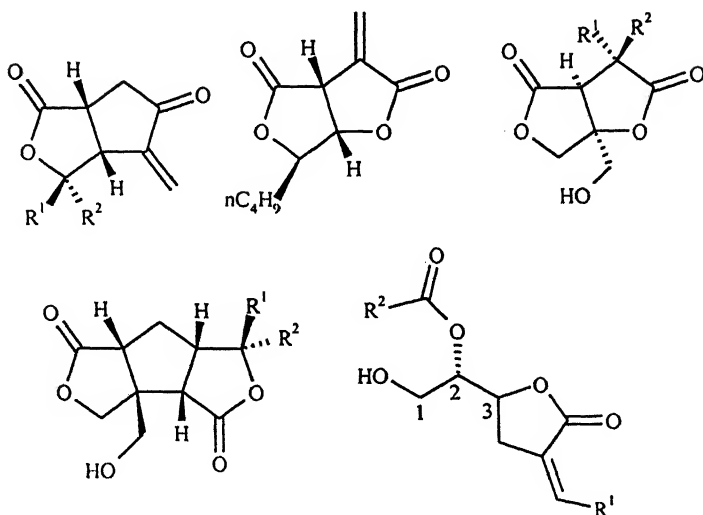
The fact that a 5-*endo*-halomethyl substituent in norbornyl  $\alpha$ -diketones conveniently affords the corresponding  $\gamma$ -lactones (Scheme 46) prompted us to design the synthesis of novel bis- $\gamma$ -lactones separated by diquinane, e.g., **127** (Scheme 48). Such bis- $\gamma$ -lactones are known to be biologically active.<sup>47-49</sup> The most interesting is when  $\text{Y}=\text{OH}$ , it is a rigid model for biologically active DAG (Diacyl Glycerol) analogues.<sup>47</sup>

**Scheme 48:** Retrosynthetic scheme for a rigid model for DAG analogue

The protein kinase C (PK-C) is an enzyme that plays a critical role in cell signal transduction after it is activated by the binding with DAG.<sup>47a</sup> Recently conformationally constrained analogues of DAG have been the focus of much interest in order of insight into “active” conformations that bind efficiently to (PK-C). Marquez synthesized several bis  $\gamma$ -lactones as molecular scaffolds for the construction of rigid diacyl glycerol (DAG) analogues. Some of those are shown in Chart 6. These compounds function as rigid DAG analogues and bind to the DAG target, PK-C, with micromolar affinities.

**Scheme 49:** Synthesis of a rigid diacyl glycerol analogue by Marquez

The synthetic scheme for one of the bis  $\gamma$ -lactone separated by a spacer cyclopentane ring between the two  $\gamma$ -lactone moieties, is depicted in Scheme 49.<sup>47b</sup>

**Chart 6:** Diacyl glycerol analogues synthesized by Marquez

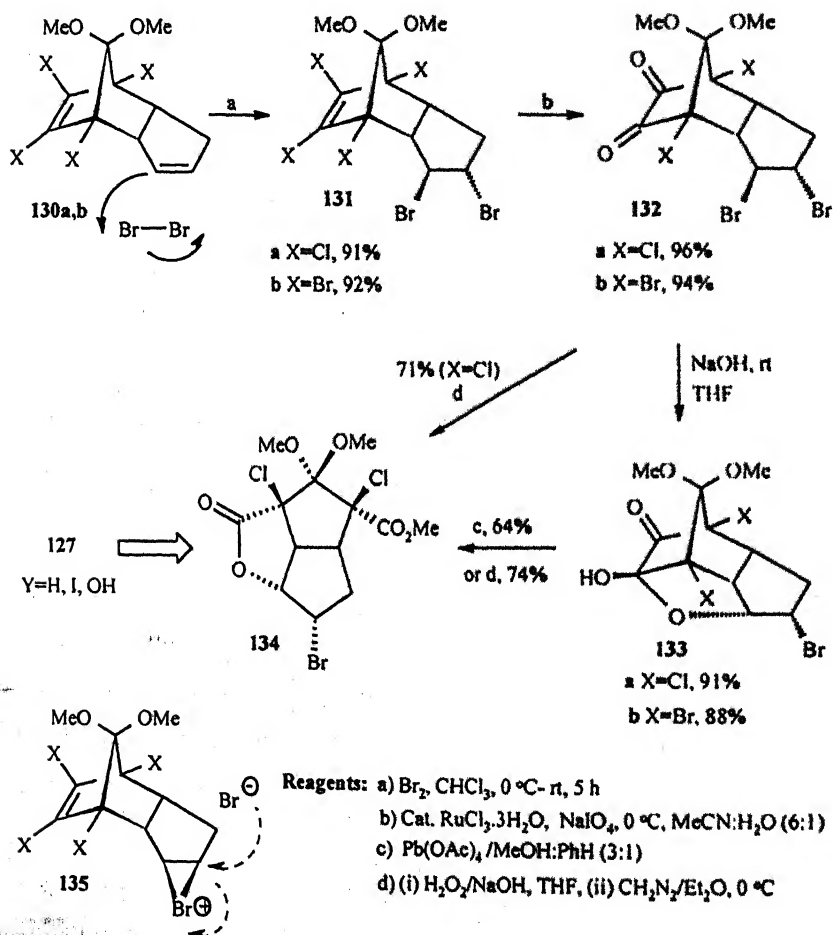
We developed a short and elegant strategy for a new rigid DAG analogue synthesis, the retrosynthetic analysis is shown in Scheme 48. An advanced precursor **128**, which is shown in Scheme 7 was synthesized in just three steps starting from easily accessible starting materials such as cyclopentadiene and tetrachloro-5,5-dimethoxycyclopentadiene **5**.

The easily available cyclopentadiene derived cycloadducts **130a,b** was brominated to give exclusively the dibromo compounds **131a,b** via trans addition of bromine to the double bond as shown in **135** (Scheme 50). The dibromo compounds were subjected to  $\text{RuO}_4$  oxidation to furnish the corresponding diketones **132a,b** in excellent yields (Scheme 50). The chloro diketone **132a** was directly cleaved using  $\text{NaOH}/\text{H}_2\text{O}_2$  using THF as the solvent to furnish the diquinane

based lactone **134** in 71% of yield. Here THF was used as the solvent instead of MeOH. The lactone **134** could serve as an advanced intermediate for the bis- $\gamma$ -lactone **127**. The hemiacetal **133a** was also

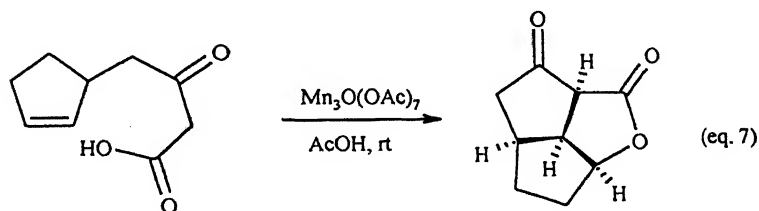
**Scheme 50: Synthesis of a diquinane based  $\gamma$ -lactone:**

A potential precursor for DAG Analogues



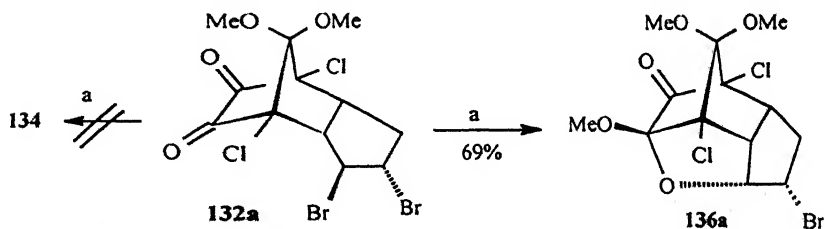
treated under both neutral lead tetraacetate and basic  $\text{H}_2\text{O}_2$  cleavage conditions to furnish the diquinane lactone **134** in high yield.

Similar type of polycyclic  $\gamma$ -lactone-fused cyclopentane ring systems (eq. 7), was synthesized by Corey by intramolecular Manganese(III) acetate assisted cyclization of acetic acid derivatives on olefins (olefin carbolactonization).<sup>49</sup>



In fact, we wanted to cleave the dibromo  $\alpha$ -dione **132a** under the normal basic cleavage condition using alkaline  $\text{H}_2\text{O}_2$  in MeOH to get the cleavage product, the lactone **134**. However, we obtained an unexpected product, the oxa-tetracyclic acetal **136a** in 69% of yield (Scheme 51).

Scheme 51

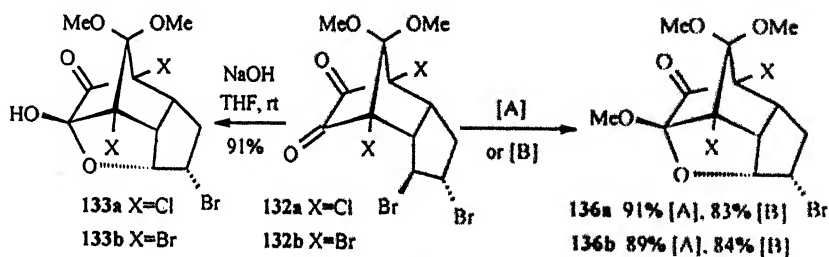


a)  $\text{H}_2\text{O}_2/\text{NaOH}, \text{MeOH}$

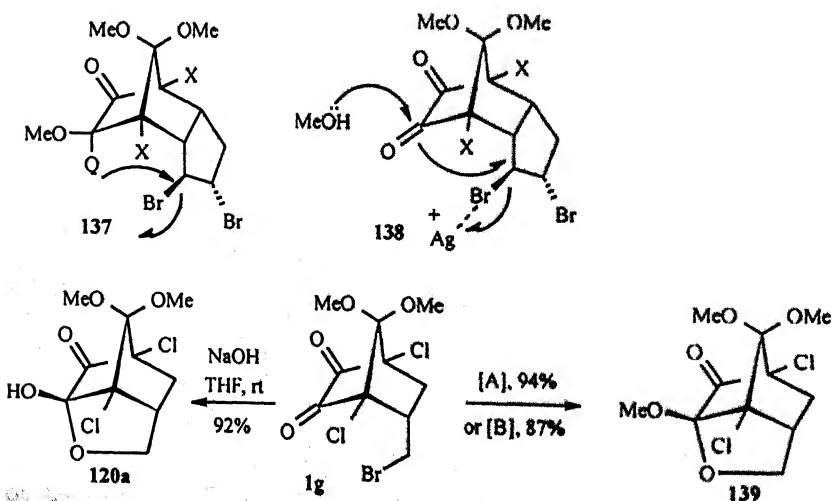
We then utilized this reaction for preparing acetals and hemiacetals. The dibromo  $\alpha$ -diones **132a,b** were subjected to 2

equivalent of 6N NaOH in MeOH as solvent leading to exclusively the corresponding acetals 136a,b in high yield (Scheme 52). Switching the solvent system to THF, excellent yields of the corresponding hemiacetals 133a,b were realized, which actually prompted us to choose THF as the solvent during the cleavage of the  $\alpha$ -dione 132a to afford the lactone 134 (Scheme 50). The acetals or hemiacetals were

Scheme 52: Ag<sup>+</sup> mediated reactions leading to acetals



[A] NaOH, MeOH, rt

[B] AgNO<sub>3</sub>, MeOH, reflux

obtained via intramolecular displacement of bromide by the alkoxide as shown in 137 for acetals (Scheme 52).

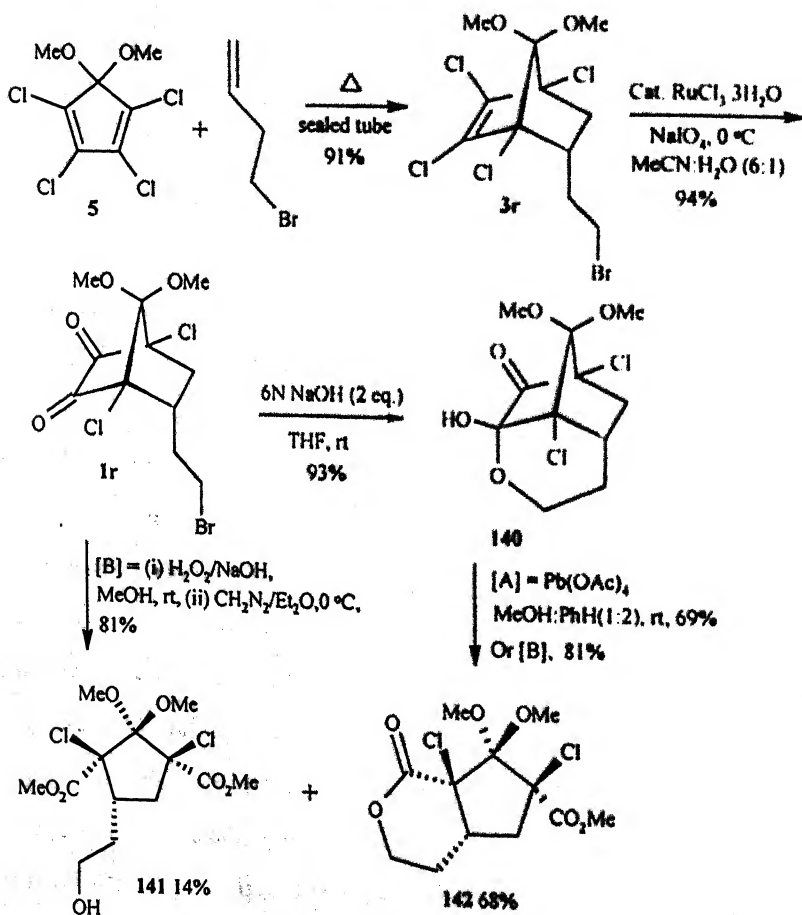
We thought that  $\text{Ag}^+$  could act as a sequestering agent as shown in 138 and possibly trigger the transformation under neutral condition, without the mediation of alkoxide or hydroxide. Indeed when the diketones 132a,b were refluxed with  $\text{AgNO}_3$  in MeOH, high yields of oxa-tetracyclic acetals 136a,b were obtained. Further, the reaction was generalized to the monosubstituted diketone 1g. Subjecting the dione 1g to  $\text{AgNO}_3$  in MeOH under reflux condition, the oxa-tricyclic acetal 139 was formed in high yield. Also under basic condition the acetal 139 and the hemiacetal 120a were prepared from the diketone 1g (Scheme 52).

**2.2 Synthesis of  $\delta$ -lactones:** The methodology was successfully extended to the synthesis of  $\delta$ -lactones by using suitable dienophiles. We prepared the adduct 3r derived from tetrachloro-5,5-dimethoxycyclopentadiene 5 and 4-bromo-1-butene in 91% yield (Scheme 53). It was oxidized to give the  $\alpha$ -diketone 1r in 94% yield. When the basic cleavage of the dione 1r was carried out, 68% of the  $\delta$ -lactone fused cyclopentane derivative 142 along with 14% of 141 possessing free hydroxyl group was isolated (Scheme 53). Under basic conditions, the initially formed  $\alpha$ -keto hemiacetal 140 exists in equilibrium with  $\alpha$ -diketone, and the latter gets cleaved with alkaline hydrogen peroxide to give diacid first. Upon acidic work up, one of the carboxylic acid group lactonizes with the free primary alcohol and the



other carboxylic acid was esterified with diazomethane, as depicted in scheme 44. The intermediate hemiacetal **140** formed in the reaction mixture, which was separately cleaved to give the lactones was also characterized. The diketone **1r** was treated with 2 equivalent of 6N NaOH in THF to furnish 93% of the hemiacetal **140** via intramolecular

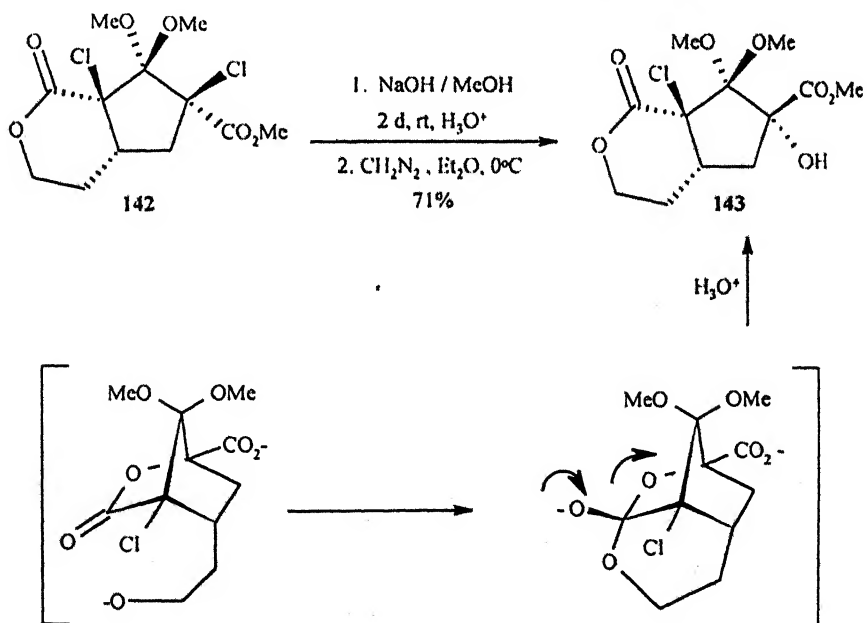
Scheme 53: Synthesis of cyclopentannulated  $\delta$ -lactone



displacement of bromine by the alkoxide (Scheme 53). The hemiacetal was separately subjected with lead tetraacetate in 2:1 MeOH and benzene, and alkaline  $\text{H}_2\text{O}_2$  to afford exclusively the  $\delta$ -lactone **142** in high yield.

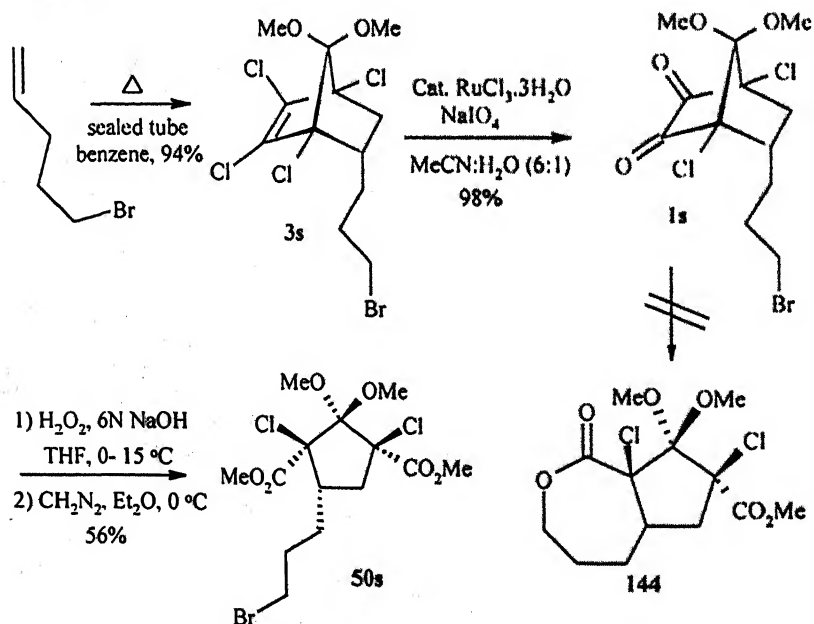
The mechanistically intriguing, lactone assisted, highly regio- and stereoselective transformation of  $\alpha$ -chloro ester to  $\alpha$ -hydroxy ester, at a sterically congested tertiary center is also feasible for  $\delta$ -lactone **142** as depicted in Scheme 54. The  $\alpha$ -hydroxy ester bearing  $\delta$ -lactone derivative **143** was obtained in 71% of yield.

**Scheme 54:** Lactone assisted regio- and stereoselective transformation to  $\alpha$ -hydroxy ester



With the hope of preparing the cyclopentannulated seven membered lactone **144** the adduct **3s** of tetrachloro-5,5-dimethoxycyclopentadiene with the higher homologue 5-bromo-1-pentene was prepared (Scheme 55). When the cleavage reaction of the diketone **1s** derived from the adduct **3s** was conducted, the cyclopentane derivative **50s** having 3-bromopropyl side chain was obtained instead of the lactone **144**. This experiment clearly demonstrates that the intramolecular displacement of bromine is possible only when it leads to a five or six membered ring, and not feasible for seven membered ring. Further, it provides concrete proof for the fact that intermolecular displacement by hydroxide was not the

Scheme 55



probable route and that only appropriate haloalkyl substituent furnishes the desired lactones.

### 3. Conclusion

In conclusion, we could successfully accomplish the  $\gamma$ -lactone-fused cyclopentane ring system in three steps from Diels-Alder adducts in excellent overall yield (51-64%). The methodology provides flexibility to use Grignard reagent to achieve numerous structurally varied systems. A short synthetic access from  $\alpha$ -diketones to  $\gamma$ - and  $\delta$ -lactones was also demonstrated. Lactone-assisted selective transformation of a  $\alpha$ -halo ester to  $\alpha$ -hydroxy ester functionality at a sterically congested tertiary center was realized both for the  $\gamma$ - and  $\delta$ -lactone. A short synthetic access from  $\alpha$ -diketones to  $\gamma$ - and  $\delta$ -lactones was demonstrated and an elegant and stereoselective strategy for a rigid DAG model was developed, an advanced intermediate for its synthesis was prepared in just three steps starting from tetrahalo cyclopentadiene adduct.

## Chapter 2

### A Concise Synthesis of Novel Oxa-bridged Compounds

#### 1. Introduction

The synthesis and chemistry of aesthetically pleasing, strained polycyclic unnatural compounds continues to fascinate and pique the imagination of chemists because of their unusual geometries, marvelous structural architecture and intriguing chemistry leading to a great deal of physical-organic, theoretical and spectroscopic investigations.<sup>50</sup> The unfavorable thermodynamic stability due to high strain which poses formidable synthetic challenge for designing a rational strategy for their creation, generated a lot of interest among synthetic chemists, and culminated in the synthesis of a wide class of strained systems, mostly carbocyclic compounds (Chart 7).<sup>51</sup> Another equally enthralling synthetic task is the preparation of relatively less explored heterocyclic strained compounds, which have started receiving considerable current interest due to the exciting as well as more useful properties exhibited by them and for a comparison of their distinctive reaction behavior with the carbocyclic analogues, a few synthesis of [n]-hetero-[n]-peristylane is discussed below (Scheme 56-59).<sup>52,56</sup> The rigid 'heterologues' decked with heteroatoms such as oxygen, nitrogen or sulfur, could serve not only as potentially promising metal binders but also as prospective building blocks for the synthesis of complex polycyclic unnatural and natural products.

Chart 7: Some aesthetically pleasing molecules



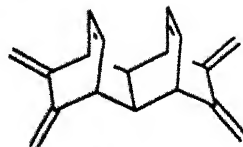
Cubane



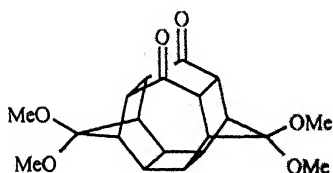
Pentaprismane



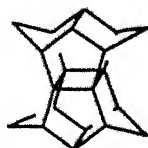
Seco hexaprismane



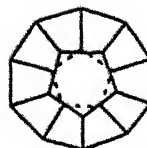
Tetracyclic hexaene



Heptaprismane analogue



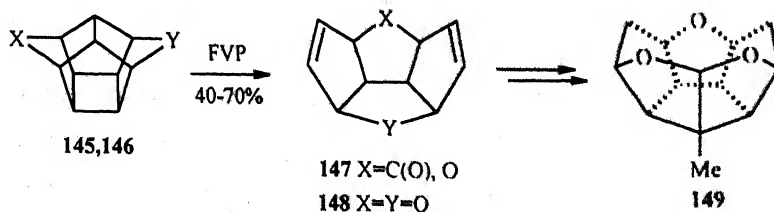
Pagodane



Dodecahedrane

A novel and expedient synthetic approach based on the regioselective thermal cyclobutane fragmentation of hexacyclo systems **145,146** leading to the corresponding oxa tetraquinanes **147,148**, was developed by Mehta, the carbonyl group of 7-ketonorbornane remains intact (Scheme 56).<sup>53</sup> The trioxa[5]-peristylane **149** was a novel extension of the oxatetraquinane **148**.<sup>54</sup>

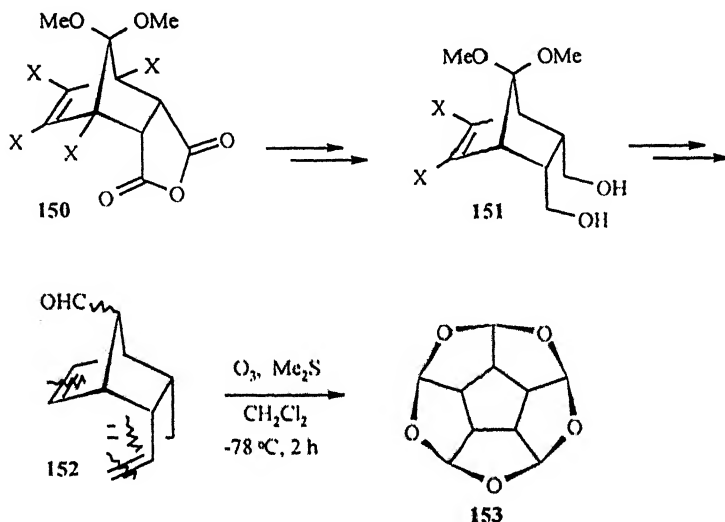
Scheme 56: Synthesis of trioxa[5]-peristylane



[n]-Hetero-[n]-peristylanes are related to the [n]-peristylanes, where the methylene groups on the rim of the 'bowl' are replaced by heteroatoms and could serve as a new class of ionophores. The first

elegant synthesis of pentaoxa[5]peristylane **153** by Mehta based on a facile cascade cyclization during ozonolysis of the aldehyde **152**.<sup>52a</sup> The synthesis begins with the conversion of maleic anhydride adduct of **150** to the key intermediate **152** through a straight forward sequence of oxidation and Wittig olefination of dehalogenated *endo*, *endo*-diol **151** (Scheme 57).

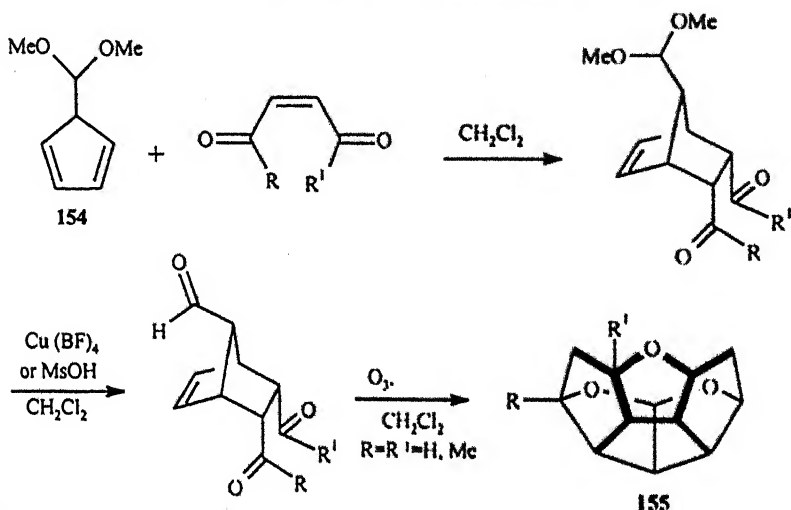
Scheme57: Synthesis of pentaoxa[5]peristylane



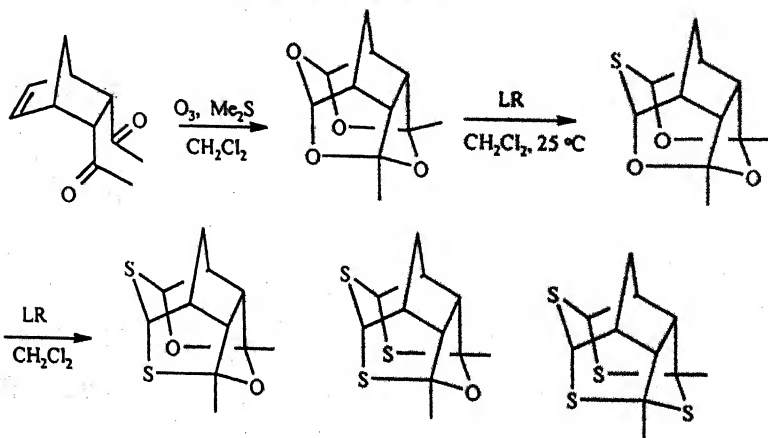
Wu and coworkers synthesized for the first time the alkyl substituted pentaoxa[5]peristylanes **155** in an overall yield of 35-45% starting from the compound **154** as depicted in Scheme 58.<sup>55</sup> They have further demonstrated the direct substitution for the oxygen atom by the sulfur atom in the reaction of the acetal groups with Lawesson's reagent (LR) leading to novel thia-cage compounds (Scheme 59).<sup>52c</sup> The oxygen atoms of tetraoxa cage compound were sequentially replaced by sulfur atoms with LR in dichloromethane at

25 °C giving mono, di, tri, and tetra thia-cage compounds as shown in Scheme 59.<sup>52c</sup> They have also accomplished the synthesis of cage compounds containing nitrogen, oxygen and sulfur in one molecule.<sup>52c</sup>

**Scheme 58:** Synthethis of alkyl substituted pentaoxa[5]peristylane



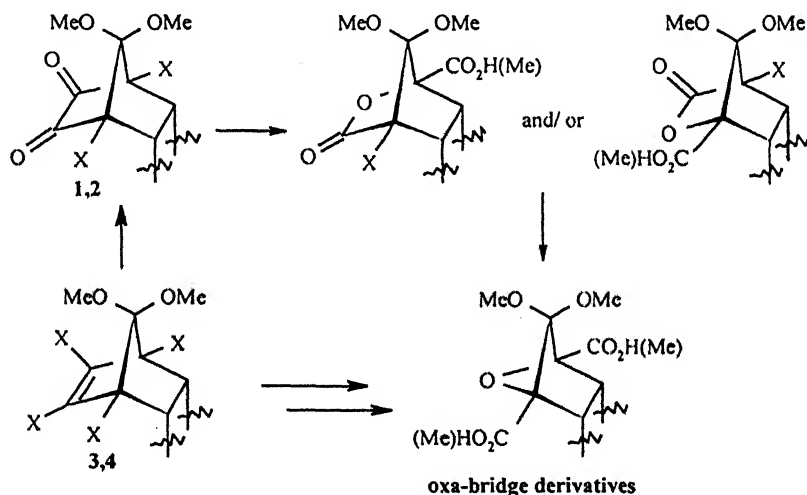
**Scheme 59:** Synthesis of thia-cage compounds





This chapter deals with a one-pot synthesis of highly oxygenated strained bis-oxa-bridged compound from the bis- $\alpha$ -diketone and generalized to other substrates, thus demonstrating that the process could be efficiently applied to replace the 1,2-dihaloalkene bridge of tetrahalonorbornyl derivatives with an oxygen bridge via the diketones, as depicted in Scheme 60.

**Scheme 60:** The replacement of dihaloalkene bridge by oxygen bridge via the diketones

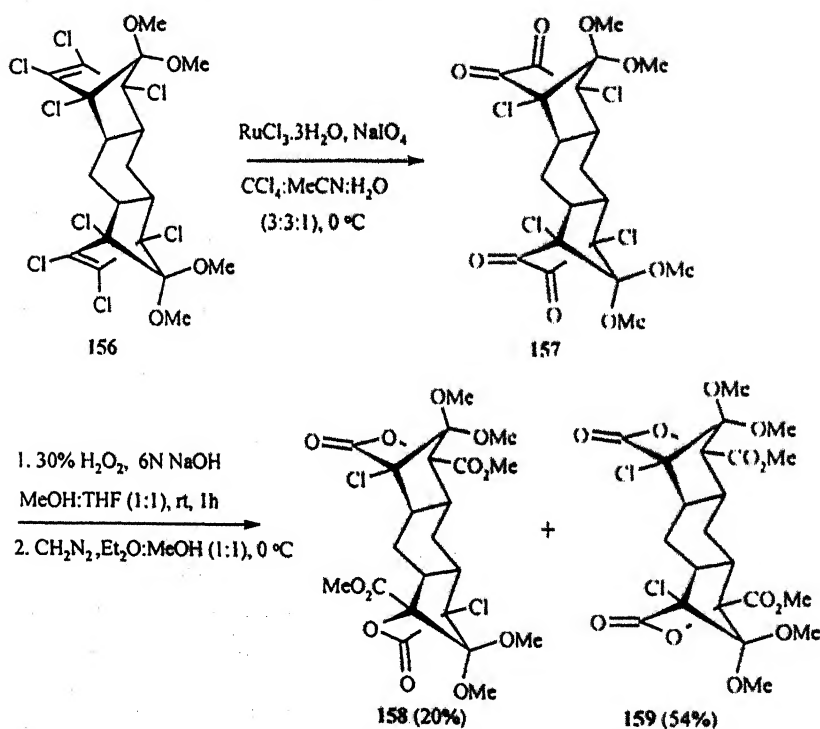


## 2. Results and Discussion

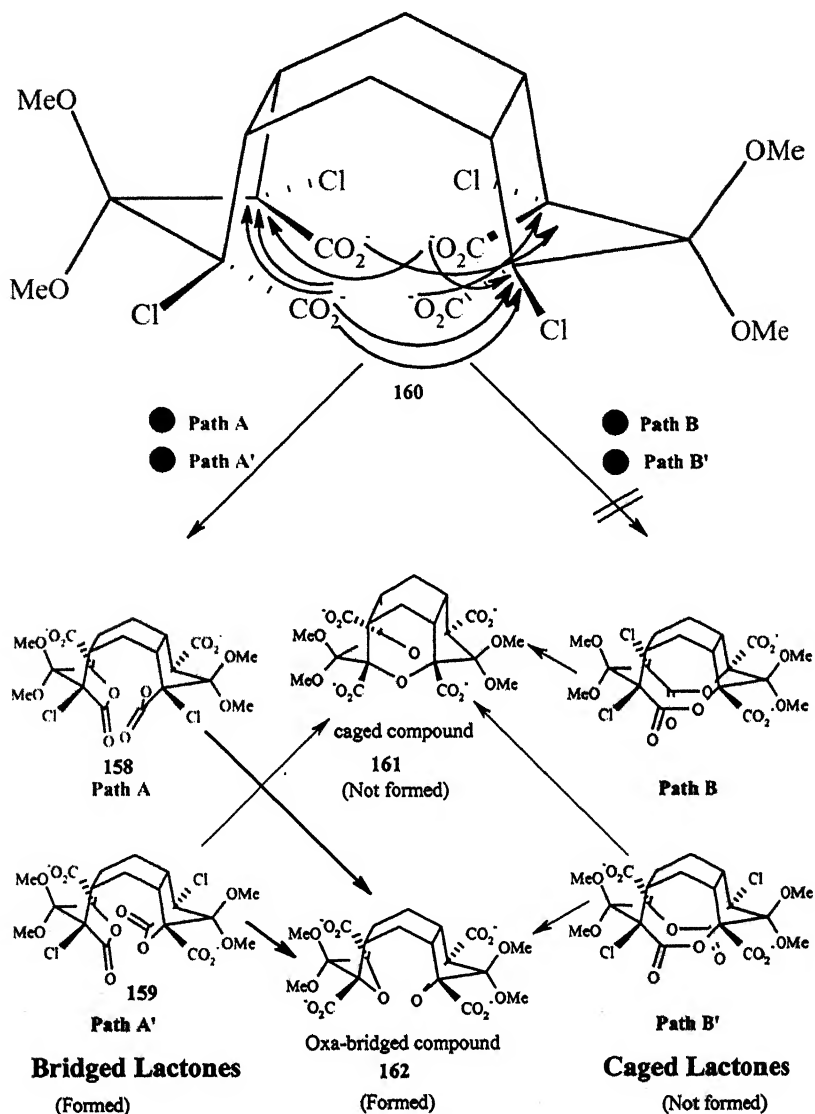
Recently we have demonstrated from our laboratory a near quantitative conversion of bis-adduct 156 to bis- $\alpha$ -diketone 157 by employing ruthenium-catalyzed oxidation (Scheme 61). Driven by the curiosity to know what would be the fate of tetracarboxylate intermediate that would be generated under the  $\alpha$ -dione cleavage

conditions, especially because of the availability of at least two intramolecularly displaceable halides for each carboxylate, the bis-diketone **157** was subjected to cleavage reaction using alkaline  $\text{H}_2\text{O}_2$ . The products formed in this reaction were isolated, characterized and assigned the regioisomeric pentacyclic lactone structures **158** and **159** (Scheme 61).<sup>13</sup>

Scheme 61: Cleavage reaction of bis  $\alpha$ -diketone **157**

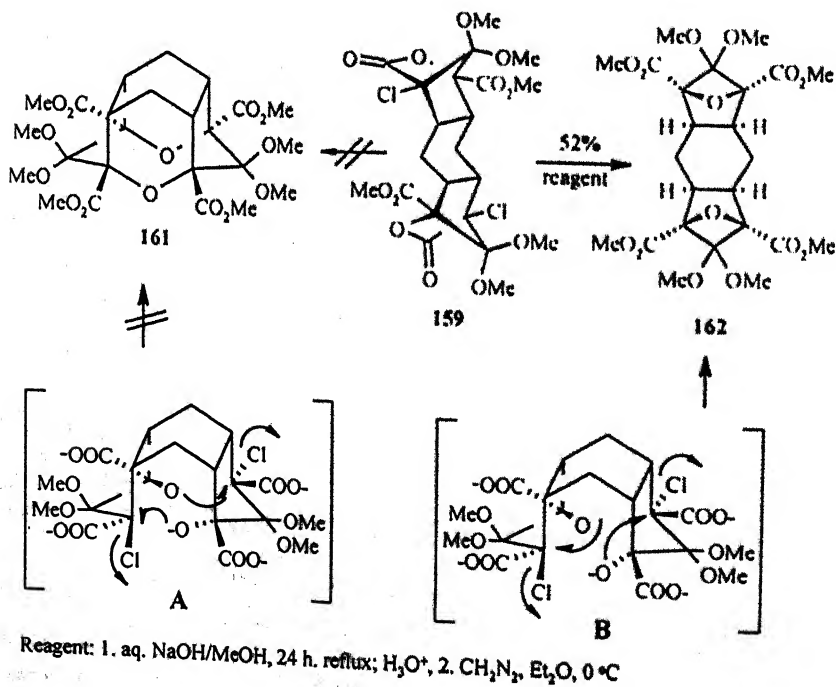


A detailed analysis of the possible pathways available for the *in situ* generated tetracarboxylate intermediate **160** is presented in Scheme 62.

**Scheme 62.** Synthesis of the novel bis-oxa-bridged compound 162

Path A or A' would lead to bridged lactones **158** and **159**, similar to those obtained in case of mono-diketones (Scheme 15), while path B or B' would lead to caged lactones via transannular displacement. Interestingly both the pairs of lactones have the potential to undergo one more iteration of  $S_N2$  displacement, under basic conditions, this time utilizing the last surviving out of the four halides, leading either to a caged or oxa-bridged compound as shown in Scheme 62.

Scheme 63. Synthesis of the novel bis-oxa-bridged compound **162**

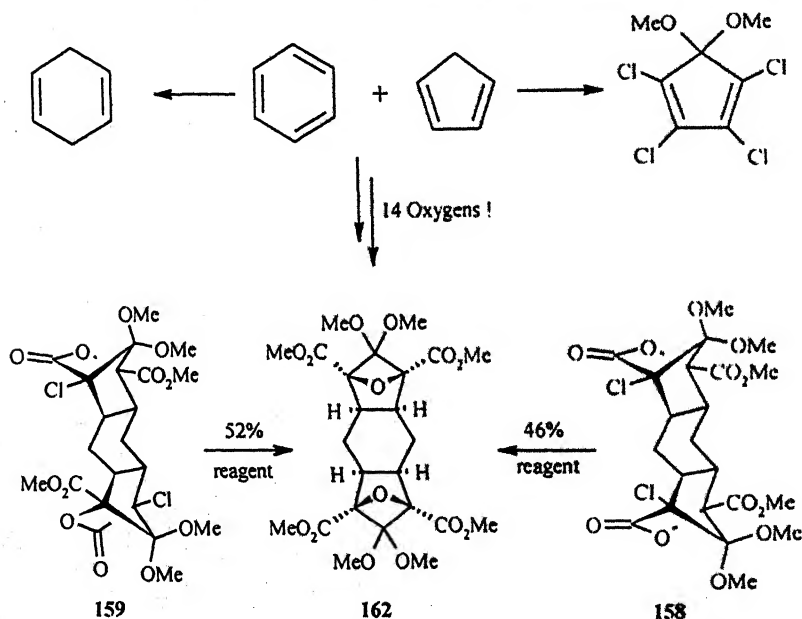


Our preliminary results<sup>13</sup> revealed that intermediate **160** leads exclusively to bridged lactones (following path A or A') in a ratio of 1:2.7 (Scheme 60). Initially the minor bridged lactone (path A') was treated with NaOH anticipating the formation of caged compound **161**. However, for our surprise oxa-bridged derivative **162** was obtained in 52% yield via intermediate A (Scheme 63) through a reiterative process which is selectively undergoing intramolecular S<sub>N</sub>2 displacement within each cyclopentane ring as depicted in Scheme 63. The structural assignment for **162** was based on single crystal x-ray analysis. It is intriguing that a reaction pathway leading to a strained oxygen bridged compound **162** was favored over the alternative that would have led to a less strained cage compound **161**.

At this point we thought of generalizing the methodology to obtain a variety of oxa-bridged compounds and to develop a one-pot procedure for the conversion of diones to oxa-bridged moiety, without the isolation of intermediate bridged lactones. Also, it is clear from the proposed mechanism that the major bridged lactone **158** (path A, Scheme 62), which is not a suitable precursor for caged compound could in principle furnish oxa-bridged derivative **162**, thus furnishing a 'chemical' proof for the structural assignment and proposed mechanism.

Indeed, when **158** was subjected to aqueous alkaline conditions followed by esterification, **162** was obtained in 46% yield (Scheme 64). The entire process essentially amounts to converting two hydrocarbons, i.e., benzene and cyclopentadiene to a highly symmetric pentacyclic bis oxa-bridged compound **162** by adding as many as 14 oxygen atoms (Scheme 64), since cyclohexadiene and tetrachloro-5,5-dimethoxycyclopentadiene were prepared from benzene and cyclopentadiene respectively.

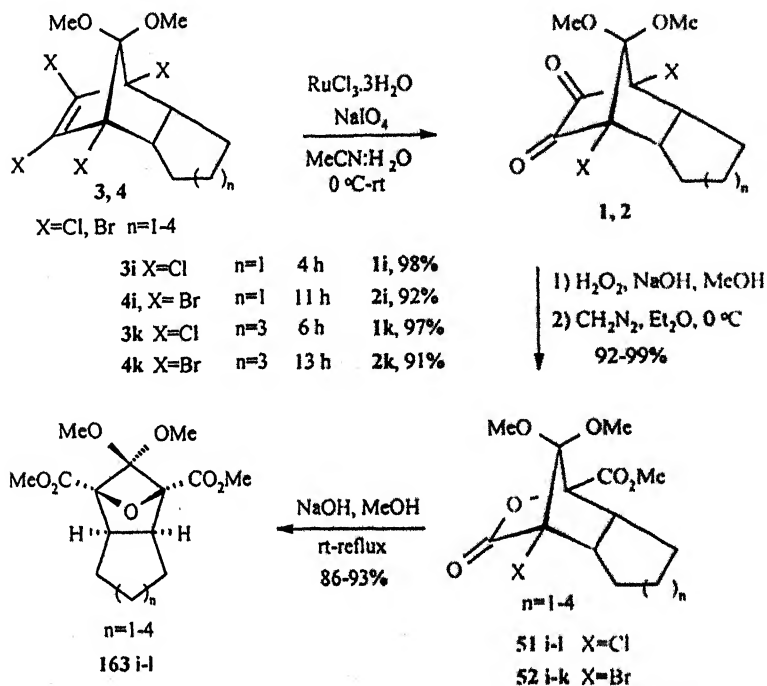
Scheme 64: Synthesis of bis-oxa-bridge derivative **162** from major lactone **158**



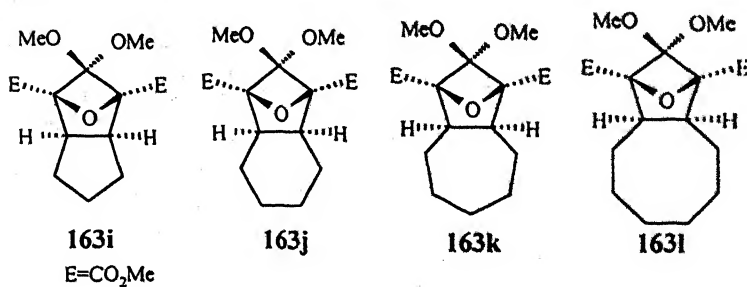
Reagent: 1. aq. NaOH/MeOH, 24 h. reflux;  $\text{H}_3\text{O}^+$ , 2.  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$

Further the methodology should be applicable to the tricyclic lactones **51,52 i-l** (Scheme 12), since intramolecular displacement

was taking place in the cyclopentane ring. The results are summarized in Table 1. A variety of bridged tricyclic lactones **51i-l** and **52i-l** were prepared from the  $\text{RuO}_4$  oxidation of the corresponding tetrahalo adducts **3i-l** and **4i-l** followed by the alkaline cleavage of the  $\alpha$ -diketones **1,2 i-l**. The tricyclic lactones **51j**, **52j** and **51l** were prepared previously in our lab. The yield and reaction time for the preparation of  $\alpha$ -diketones **1i,l** and **2 i,l** from the corresponding adducts are shown in Scheme 65. When the tricyclic lactone **51j** was refluxed with aqueous NaOH in MeOH for 18 h, the corresponding oxabridge derivative **163j** was formed in 89% of yield (entry 3, Table 1). The methodology was generalized for a number of tricyclic lactones **51i-l** and **52i-l** employing chloro and bromo derivatives to obtain the oxa-bridged compounds **163i-l** in high yield (Scheme 65, Table 1). The reaction condition for bromo lactones **52i-k** was even optimized at room temperature to furnish the corresponding oxa-bridge derivatives in excellent yields (Table 1, entry 2, 4, 6). The  $^1\text{H}$  NMR spectrum of the oxa-bridge derivatives showed three singlets, two for OMe and one for both the methyl esters (3.81-3.82 ppm). In  $^{13}\text{C}$  NMR spectra of **163i-l**, a single peak at ~167 ppm was observed for the ester carbonyl while the oxa-bridge bearing carbons showed a diagnostic peak in the range of 91.1-93.7 ppm.

Scheme 65: Synthesis of tricyclic oxa-bridged derivatives 163 i-l<sup>a</sup>

<sup>a</sup> The precursors 1,2 for 51, 52 j and 51l are not shown as they were previously prepared and reported by us. A detailed discussion for 51, 52 i and 51, 52 k is given under the scheme 78 and 81



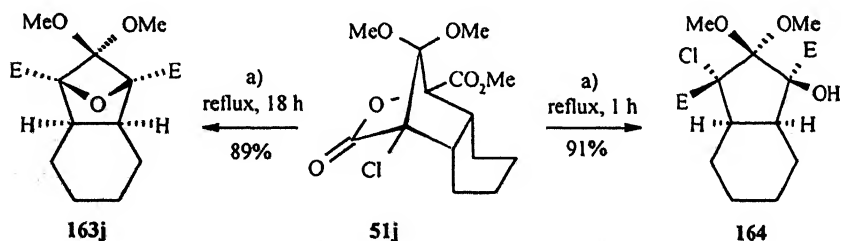


**Table 1:** Preparation of oxa-bridge derivatives **163i-l** from bridged lactones **51**, **52i-l**.

entry	substrate, X, n	temp.	time	yield (%)	product
1	<b>51i</b> Cl 1	reflux, 16 h		86	<b>163i</b>
2	<b>52i</b> Br 1	rt, 28 h		88	
3	<b>51j</b> Cl 2	reflux, 18 h		89	<b>163j</b>
4	<b>52j</b> Br 2	rt, 24 h		90	
5	<b>51k</b> Cl 3	reflux, 18 h		88	<b>163k</b>
6	<b>52k</b> Br 3	rt, 24 h		93	
7	<b>51l</b> Cl 4	reflux, 20 h		92	<b>163l</b>

However giving less reaction time, i.e., refluxing for one hour the chloro lactone **51j** was stereoselectively transformed to the  $\alpha$ -hydroxy ester derivative **164** in 91% of yield (Scheme 66). So depending on reaction time we could able to synthesize either the  $\alpha$ -hydroxy ester derivative or the oxa-bridge compound.

**Scheme 66:** Synthesis of  $\alpha$ -hydroxy ester derivative **164**



a) 1. aq. NaOH/MeOH, 24 h. reflux, 2.  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ ,  $0^\circ\text{C}$

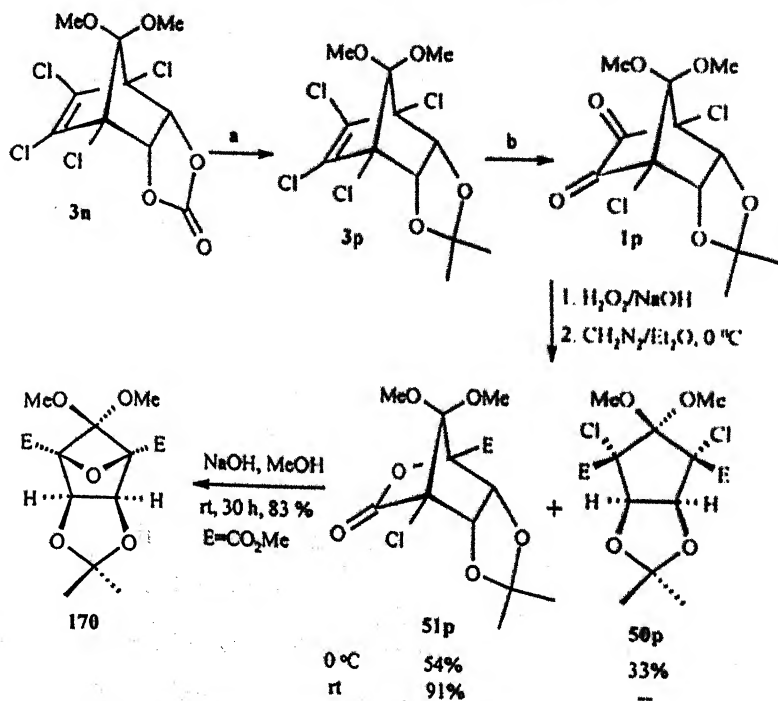
and a 9-line  $^{13}\text{C}$  NMR spectrum indicates the symmetrical nature of the product **166**.

The oxa-bridge derivative **169** with a substituent on the cyclic dienophile part could be easily derived from the bridged lactone **168** via the  $\alpha$ -dione **167**. The  $^1\text{H}$  NMR spectrum of chloro lactone **168** showed three singlets (two for OMe and one for methyl ester) and the chlorine-bearing bridgehead carbons appeared at 76.3 ppm in  $^{13}\text{C}$  NMR spectrum. The bridgehead carbon bearing the ester group was assigned at 85.6 ppm. The  $^1\text{H}$  NMR spectrum of oxa-bridge derivative **169** showed a singlet for both the ester groups at 3.28 ppm. The ester carbonyls and the oxygen bearing carbons appeared at 167.2 ppm and 90.6 ppm respectively in  $^{13}\text{C}$  NMR spectrum. The symmetrical nature of **169** was evident from a 10-line  $^{13}\text{C}$  NMR spectrum.

The methodology was successfully applied for the preparation of the oxa-bridge derivative **170**, where each carbon atom of the cyclopentanoid is connected to an oxygen atom, i.e., a fully oxygenated cyclopentanoid core starting from vinylene carbonate adduct **3n** (Scheme 68).<sup>56</sup> The chloro derivative **3n** was deprotected using  $\text{K}_2\text{CO}_3$  in MeOH and then reprotected as acetonide **3p** using amberlyst-15 in acetone (compare with Scheme 30 of Chapter 1A, page no. 40). The acetonide was smoothly transformed to the  $\alpha$ -diketone **1p** in near quantitative yield. The diketone **1p** was subjected under alkaline  $\text{H}_2\text{O}_2$  cleavage to furnish exclusively the chlorolactone **51p** at room temperature, while conducting the

reaction at 0 °C for 1 h, the cyclopentane derivative **50p** was formed in 33% of yield along with the lactone **51p** in 54% of yield. The bridged lactone **51** was refluxed under aqueous alkaline condition to furnish the oxa-bridge compound **170** in 83% of yield. The mixture of compounds **50,51p** was also subjected under same condition to give the oxa-bridge derivative **170**.

Scheme 68: Synthesis of a fully oxygenated cyclopentanoid **170**

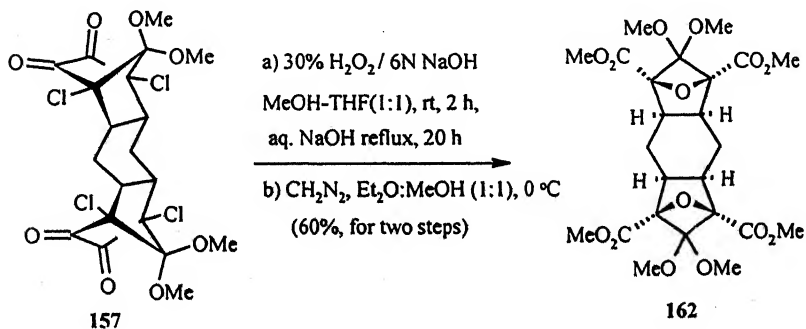


The  $^1\text{H}$  NMR spectrum of **170** exhibited 6 singlets, with both the ester groups appearing at 3.86 ppm. The oxygenated derivative

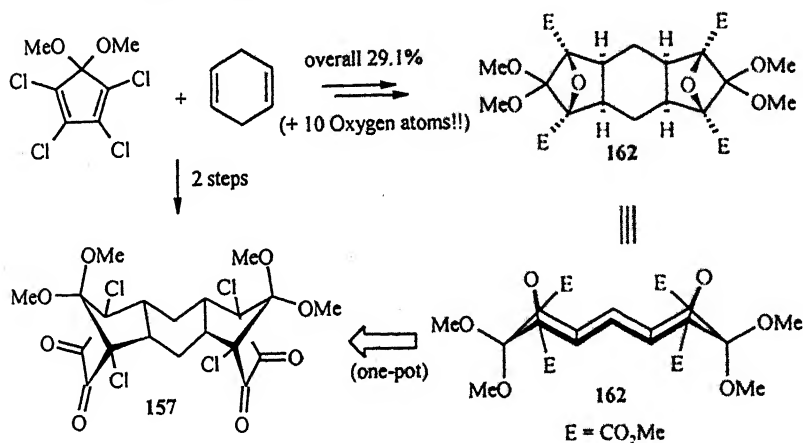
**170** showed a 10-line  $^{13}\text{C}$  NMR spectra, in which both the oxa-bridge bearing carbons appeared at 89.3, slightly shielded than other oxa-bridge compounds.

**2.1 One pot synthesis of oxa-bridge derivatives:** After successfully demonstrating the smooth transformation of bridged bicyclic lactones to the oxygen bridged compounds, the next logical step was to develop a one-pot sequence directly from the diketone without the isolation of the intermediate bridged lactones. We started with the bis-diketone **157**, which is the precursor for both **158** and **159**. Treatment of **157** with aqueous alkaline  $\text{H}_2\text{O}_2$  in MeOH-THF, initially at room temperature, and then at reflux temperature followed by esterification gave the product **162** in 60% overall yield (Scheme 69). Thus, **162** was prepared in just 3 steps with an overall yield of 29.1% starting from tetrachloro-5,5-dimethoxycyclopentadiene and 1,4-cyclohexadiene (Scheme 70). The two *syn* oxa-bridges in **162** constrain the central cyclohexane ring into boat form.

**Scheme 69:** Development of one pot procedure



**Scheme 70:** The two *syn* oxa-bridges fixe the cental cyclohexane ring into boat form

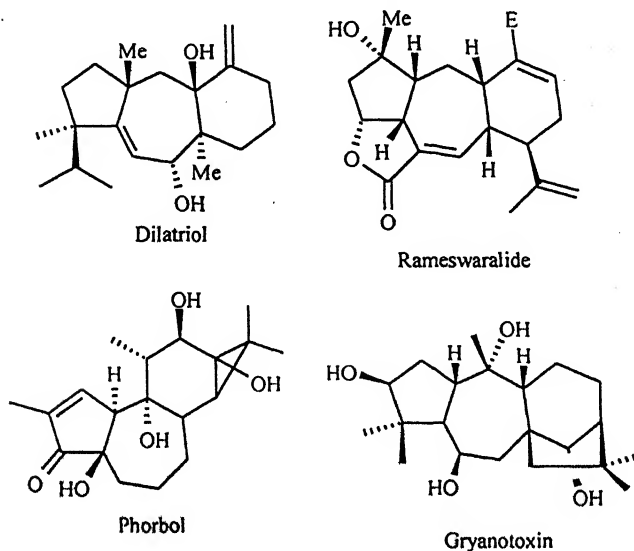


Polycyclic natural products containing a hydroazulene substructures such as dilatril, rameswarilide, phorbol, and guanacastepene A (Chart 8), represents interesting and yet demanding synthetic challenges and stimulate the development of new methodologies.<sup>57</sup> The presence of hydroazulene ring systems in biologically active natural products (Chart 8), attracted our attention to study the 2:1 adduct of cycloheptatriene 171 (Scheme 71).

The *endo,syn,endo*- bis adduct 171 of tetrachloro-5,5-dimethoxycyclopentadiene and cycloheptatriene was prepared according to the literature procedure.<sup>58</sup> To our knowledge, this adduct has not been used so far for any synthetic application. We first hydrogenated 171 to obtain 172 which was then treated with 12 mol% RuCl<sub>3</sub>·3H<sub>2</sub>O, 2.5 equivalent of NaIO<sub>4</sub> in 6:6:1 MeCN:CCl<sub>4</sub>:H<sub>2</sub>O at room temperature for 30 h to furnish a near

quantitative yield of yellow crystalline bis  $\alpha$ -diketone **173** (Scheme 71).

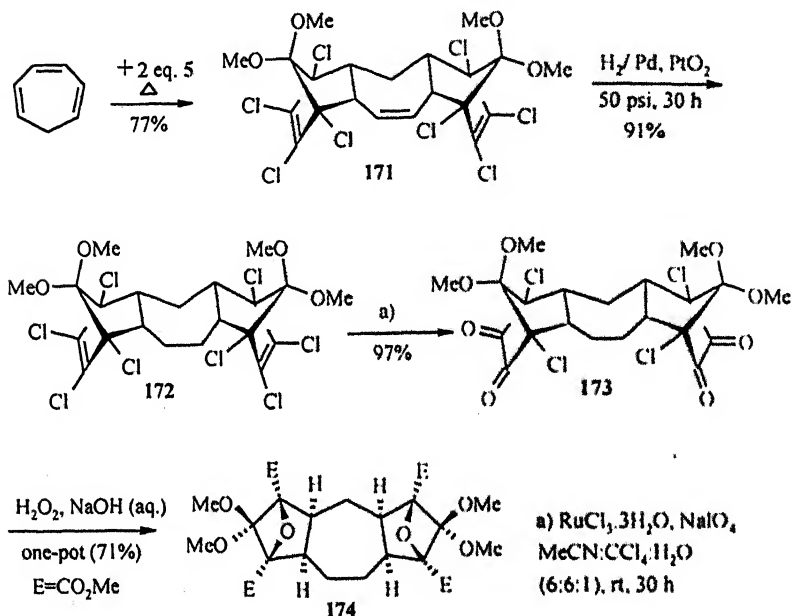
**Chart 8:** Natural products containing hydroazulene substructures



One pot transformation of bis diketone **173** to bis-oxa-bridge derivative **174** was achieved in 71% of yield. In case of the highly symmetric bis-oxa-bridge derivative **162**, the four methyl ester groups appeared as a singlet at 3.80 ppm, while two singlets at 3.80 and 3.78 ppm were seen for the substrate **174** in  $^1\text{H}$  NMR in accordance with the reduced level of symmetry in the latter. The two sets of peaks at 3.46 and 3.30 ppm were assigned for the four OMe groups of **174**. Similarly in  $^{13}\text{C}$  NMR, a single peak was observed at 166.5 ppm for all the ester groups for **162**, while the compound **174** exhibits two peaks at 166.6 and 166.4 ppm. The diagnostic four carbons bearing the oxygen bridge as well as the ester groups for **174**

appeared as two sets at 92.9 and 92.1 ppm, whereas a single peak was seen at 91.6 ppm for **162**. The molecule contains a core of *cis*, *syn*, *cis*- 5-7-5-ring system and the oxygen bridges are *syn* to each other.

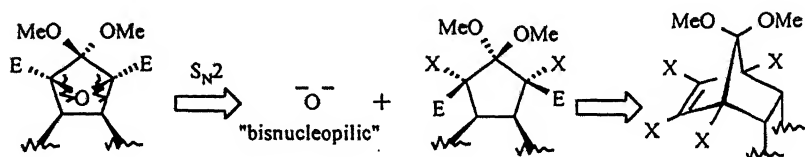
**Scheme 71:** Synthesis of bis-oxa-bridge **174** derivative from cycloheptatriene bis-adduct **171**



The synthetic sequence leading to oxa-bridge derivatives depicts a beautiful orchestration of selective utilization of the two sets of chlorines along with an illustration of an unprecedented example of extracting fullest advantage of geometric constraints on the reactivity of the molecule. In contrast to all the applications known so far of tetrachloro norbornyl derivatives where complete dechlorination is invariably followed, the availability of 'retained'

bridgehead chlorines by our method, facilitate smooth incorporation of oxa-bridges in a stepwise manner through a formal 'bisnucleophilic' oxygen as shown in Scheme 72. This demonstrates that the 1,2-dihaloalkene bridge of tetrahalonorbornyl derivatives is a useful surrogate for the oxygen bridge via the  $\alpha$ -diketone.

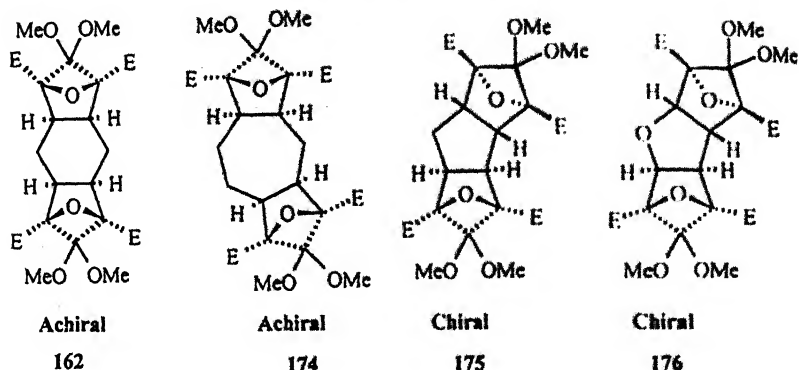
**Scheme 72:** Schematic representation of incorporation of formal "bisnucleophilic"(hypothetical) oxygen leading to oxa-bridged derivatives



The establishment of an elegant and stereoselective strategy to replace the 1,2-dihaloalkene bridge by the oxygen bridge encouraged us to design some rigid molecular scaffolds which could act as smart molecules upon suitable elaboration (Chart 9). We could incorporate interesting variations in the structure of rigid molecular scaffolds; not only we can have highly symmetric molecules **162** and **174** with both the oxygen atoms on one side but also "kinked structure" such as **175** with oxygen bridges on opposite face, separated by a central cyclopentane ring. Further, replacing the methylene of central five membered ring by oxygen atom would provide a molecule **176**, with a perfect crown component of three oxygen atoms separated by two ethylene bridges predisposed in a well defined structure.



Chart 9: Design of Novel Molecular Scaffolds: Smart Molecules

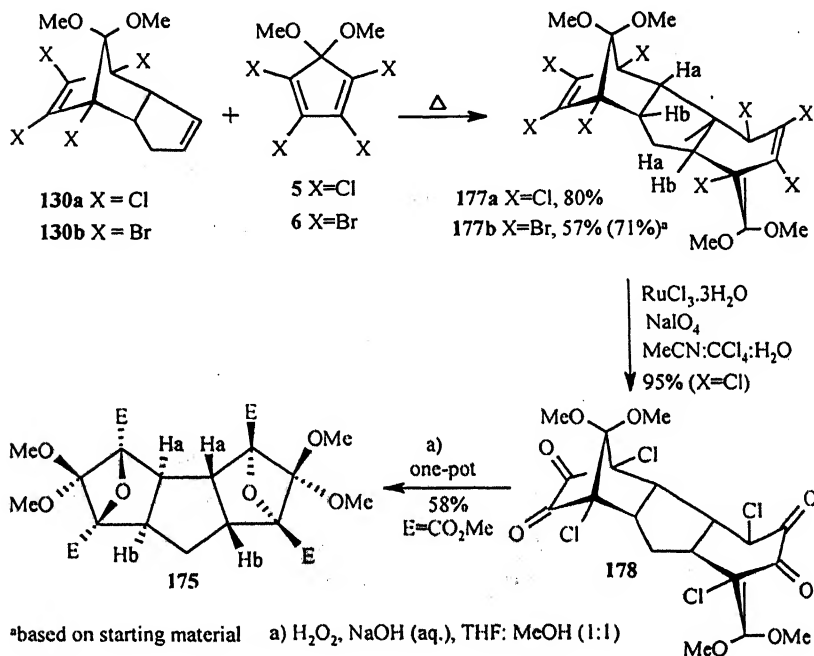


The first molecule (162 in Chart 9) is highly symmetric, thus achiral, the second molecule 174, although not as symmetric as the first one, but still achiral because of the  $\sigma$ -plane passing through it. The anti oxa-bridge nature of the third 175 and fourth molecule 176 has important consequences with regard to its structure and properties, e.g., now these molecules, although  $C_2$ -symmetric are chiral. Both the molecule possesses handedness, and we believe this will open up a newer avenue to design chiral catalyst such as crown ethers for phase transfer catalysis, which are docked on rigid molecular scaffolds.

**2.2. 2:1 adduct of tetrachloro-5,5-dimethoxy cyclopentadiene with cyclopentadiene:** We for the first time prepared and studied the 2:1 adduct of cyclopentadiene with tetrahalo dimethoxy cyclopentadiene 5 (Scheme 73). The tetrahalo cyclopentadiene monoadducts 130a and 130b were further treated with 1 equivalent

of **5** and **6** in benzene in a sealed tube for 48 h to furnish the *endo,anti,endo*- adducts **177a** and **177b**, unlike the cyclohexadiene and cycloheptatriene bis-adducts of **5**.

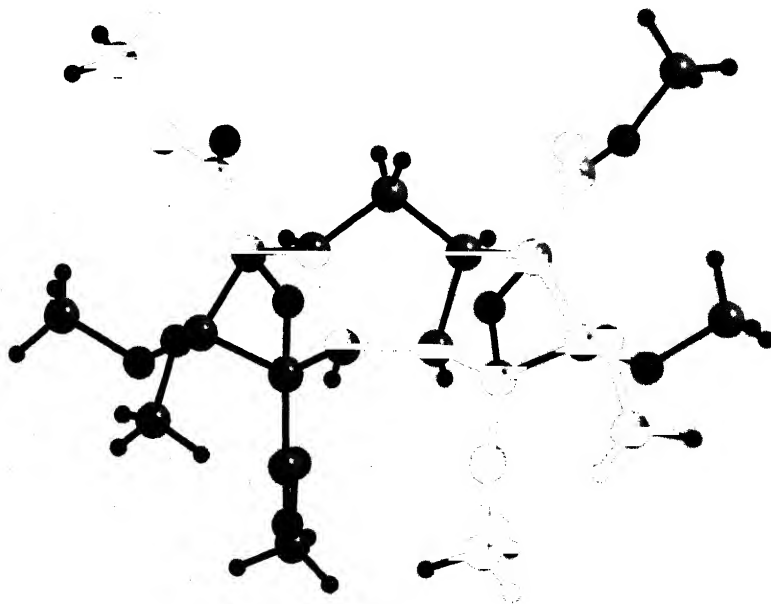
Scheme 73: Synthesis of *anti* oxa-bridge derivative **175**



In the <sup>1</sup>H NMR spectrum of adducts **177**, two singlets appeared for four OMe groups and two sets of equivalent peaks were observed for four methine protons. Two methine protons (H<sub>a</sub>) gave a doublet at 2.99 and 3.17 ppm, the other two methine protons (H<sub>b</sub>) showed a doublet of a doublet at 3.13 and 3.25 ppm, and the two methylene protons appeared as a triplet at 1.77 and 1.88 ppm for chloro and bromo derivatives respectively. Similarly in <sup>13</sup>C NMR two sets of bridgehead carbons appeared at 77.9, 77.1 ppm for chloro

adduct **177a**, and at 71.4, 71.1 for bromo analog **177b**. The chloro adduct **177a** was smoothly transformed to the corresponding bis-diketone **178** in 95% of yield.

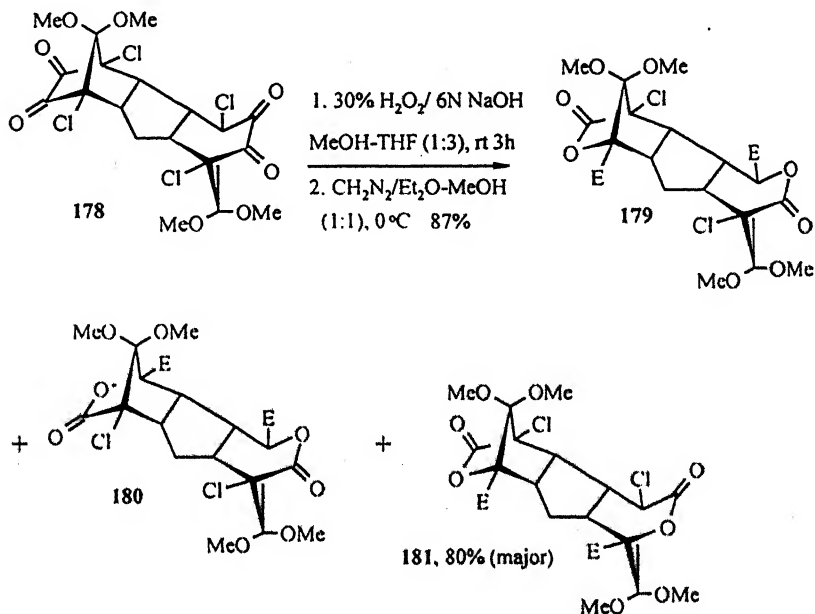
**Figure 3:** Diamond picture of *anti*-oxa bridge derivative **175**; gold (carbon), red (oxygen) and blue (hydrogen).



The bis-diketones **178** (Scheme 73), and **183** (Scheme 75) were prepared by employing 12 mol%  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$ , 2.5 equivalent of  $\text{NaIO}_4$  in  $\text{MeCN}:\text{CCl}_4:\text{H}_2\text{O}$  (12:12:1) at room temperature for 24 h to furnish a near quantitative yield of yellow crystalline product. Because of the insolubility of the bisadducts **177a** and **182**  $\text{CCl}_4$  was used in addition to  $\text{MeCN}:\text{H}_2\text{O}$  and the amount of solvent was doubled compared to the bis dione preparation of **173** (Scheme 71). The one-pot procedure was generalized for the symmetrical,

pentacyclic bis-diketone **178** to achieve the strained *anti*-oxa bridge derivative **175** (Scheme 73). We unambiguously established the structure of the *endo*, *anti*, *endo*- adducts **177** and the *anti*-oxa bridge derivative **175** by the X-ray crystal structure of **175** (Figure 3).

**Scheme 74:** Cleavage reaction of bis  $\alpha$ -diketone **178**



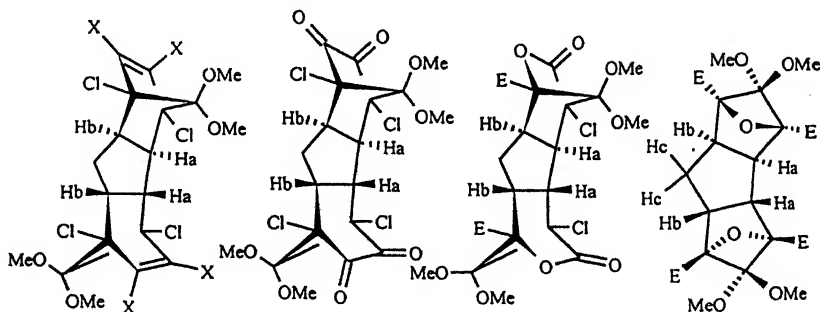
Fascinated by the number of theoretically possible pentacyclic lactones that would be obtained from the unsymmetrical bis-diketone **178** and also the utility of the resulting *endo*, *anti*, *endo* pentacyclic bis lactones as prospective building blocks for the *cis*:*anti*:*cis* triquinanes, we carried out the cleavage reaction of **178**. Interestingly, out of the three theoretically possible isomers **179**, **180**

and **181**, only one i.e., **181** was predominantly formed and isolated in 80% of yield (Scheme 74).

From the extensive  $^1\text{H}$  and  $^{13}\text{C}$  NMR studies we concluded that the major lactone could be either **180** or **181**, clearly ruling out structure **179**. It was not possible, at this stage, for us to figure out which is which, i.e. the isolated product is **180** or **181**? Both the structures are configurationally quite alike for an easy distinction by routine NMR, e.g., both the chlorine atoms are present on the same side as that of the carbonyl of lactone bridge and both the ester groups are present on the same side as the oxygen of the bridged lactone, in both the cases. The only difference between the two structures **180** and **181** is the location of the methylene of the central cyclopentane ring; whether it is located on the ester side or the chlorine side? The isolated compound clearly showed lactone and ester peaks in IR spectrum at 1800 and 1740  $\text{cm}^{-1}$  respectively. The compound exhibited three singlets, one at 3.83 for both the ester groups, two at 3.58 and 3.69 for two pairs of OMe groups in the  $^1\text{H}$  NMR spectrum. The two sets of methine protons appeared at 3.70 as a doublet of doublet and at 2.99 as a doublet. The methylene proton appears at 1.92 ppm as a triplet. The bridgehead carbons, two bearing chlorines and the other two bearing ester groups appeared at 75.0 and 86.3 ppm respectively in  $^{13}\text{C}$  NMR spectrum. A comparison of  $\text{H}_a$ ,  $\text{H}_b$  and  $\text{H}_c$  values of **175**, **177**, **178** and **181** is listed under Chart 10. Which suggests that the two  $\text{H}_a$  protons of **181** are more towards

chlorine side (comparing with the adduct 175) and two  $H_b$ 's are towards ester side (comparing with the oxa-bridge compound 175).

**Chart 10:** Comparison of  $H_a$ ,  $H_b$  and  $H_c$  values

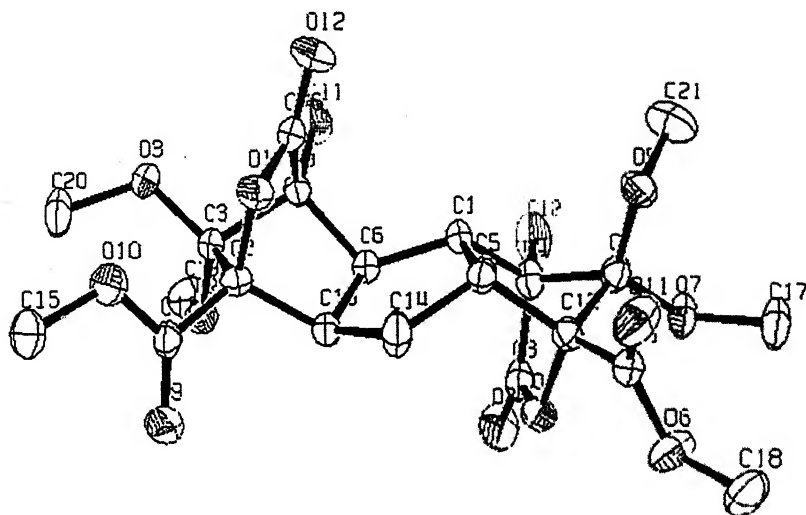


	177	178	181	175
$H_a$	2.99	2.89	2.99	3.04
$H_b$	3.13	3.19	3.70	3.46
$H_c$	1.77	1.66	1.92	1.72

$H_a$ ,  $H_b$ ,  $H_c$  values are in ppm

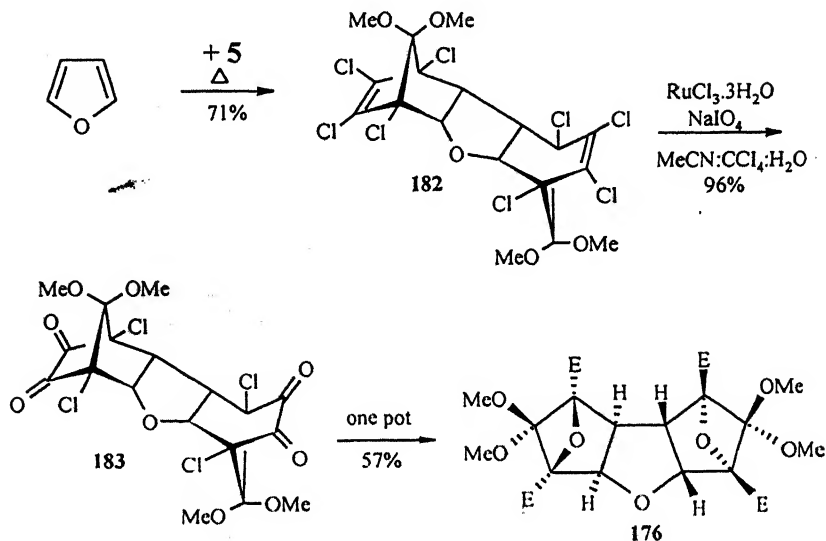
However, a single crystal X-ray analysis was carried out to unambiguously prove the structure of the bridged lactone, which is shown in Figure 4, clearly indicates that the methylene of the central cyclopentane ring is on the side of esters, i.e., **181** was exclusively formed in a highly regio and stereoselective manner. However, the crude reaction mixture of the lactones, which presumably contained traces of **180**, was treated to furnish the oxa-bridge compound **175** in 63% of yield.

**Figure 4:** ORTEP diagram of *endo,anti,endo* pentacyclic bis lactone **181**. Hydrogen atoms are excluded for clarity.



**2.3. 2:1 adduct of tetrachloro-5,5-dimethoxy cyclopentadiene with furan:** We also studied the previously overlooked 2:1 adduct **182** of tetrachloro-5,5-dimethoxycyclopentadiene **5** with furan.<sup>59</sup> The adduct was prepared by heating 2 equivalents of diene **5** with 5 equivalent of furan in benzene at 130-140 °C for 48 h in a sealed tube. We envisioned that a bis- $\alpha$ -diketone **183**, resulting from the oxidation of **182** in near quantitative yield, would have wide synthetic applications due to its unique topology as well as functional group disposition. Subjecting **183** to one-pot reaction conditions smoothly transformed it into the novel  $C_2$ -symmetric pentacycle **176** (Scheme 75). Figure 5 presents the X-ray structure of the molecule **176**.

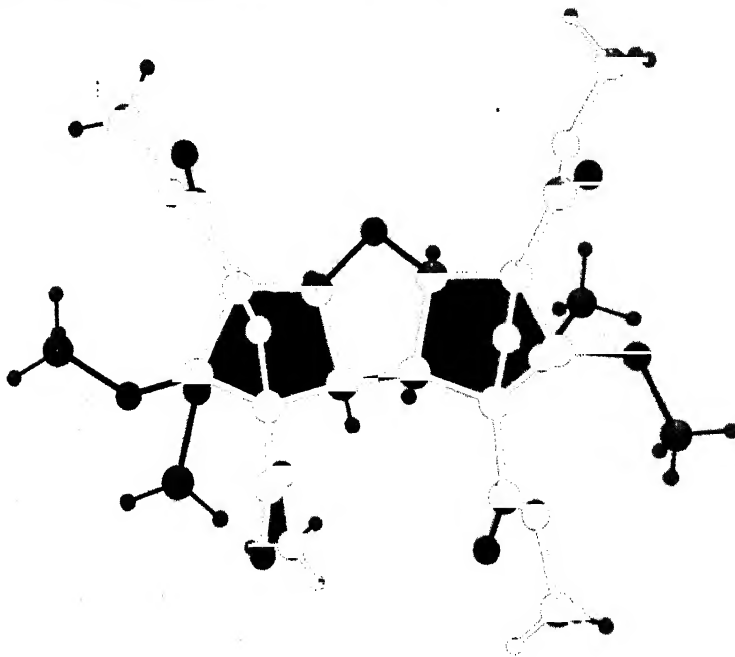
**Scheme 75:** Synthesis of anti oxa-bridge derivative **176** from furan bis-adduct **182**



The *anti*-oxa-bridge compound **176** could function as a multifunctional molecule embodied with three important substructures as shown in Chart 11. The molecule contains a perfect crown component with three oxygen atoms separated by two ethylene bridges **184** (Chart 11) and the central oxygen is equidistant to the other two oxygen atoms on opposite faces as mentioned previously. The synthesis of structurally organized polyethers that have a preexisting disposition for strong metal ion binding continues to be the focus of much research.<sup>60</sup> The molecule **176** comprises a *cis:anti:cis* fused tris-THF core **185**. The POV ray diagram for the *cis:anti:cis* fused tris-THF core of **176** is shown in Figure 6.



**Figure 5:** Diamond picture depicting *anti*-oxa bridge derivative 176; gray (carbon), red (oxygen), cyan (hydrogen).

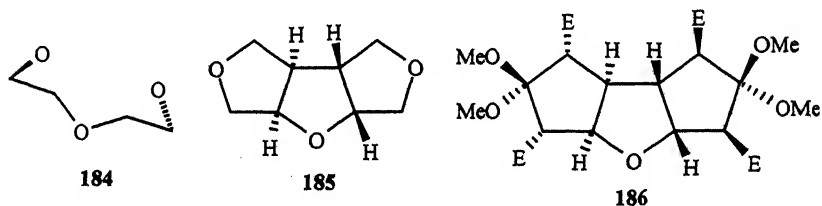


The polyethers containing five or three THF rings are known to exhibit ionophoric functions and cytotoxicities.<sup>61</sup> Also the molecule 176 comprises of a highly functionalized *cis:anti:cis* oxa-triquinane substructure 186, which receives current interest and attention. While a number of methods have been developed for the synthesis of triquinanes, only few methods are known for oxa-triquinanes or other hetero analogues of triquinane.<sup>62</sup>

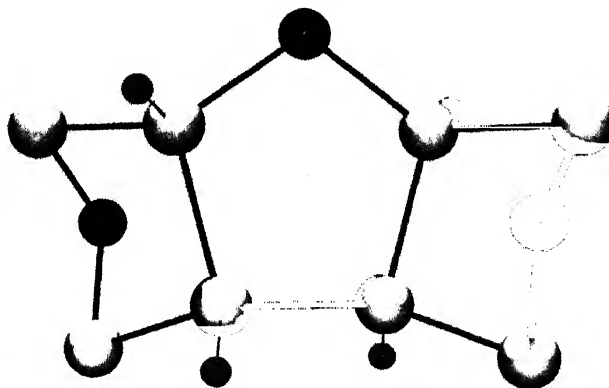
The *anti*-oxa bridge compounds 175 and 176 exhibited two sets of singlet peaks for four methyl esters and two sets of singlets for the four OMe groups, similar to *syn*-oxa bridge derivative 174. In

$^{13}\text{C}$  NMR, the four diagnostic carbons bearing the oxygen bridge as well the ester groups appeared as two sets, similar to **174** at 92.7, 90.9 ppm for **175** and 91.7, 90.9 ppm for **176**.

**Chart 10:** Substructures present in anti-oxa-bridge compound **176**



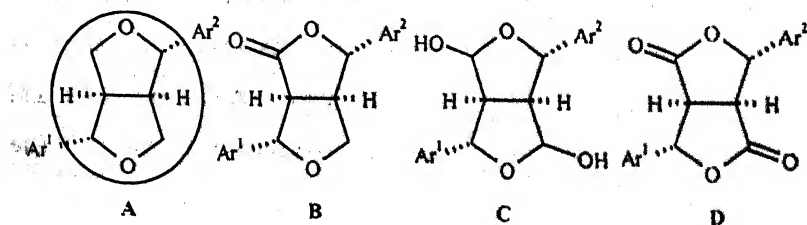
**Figure 6:** POV ray diagram for the *cis:anti:cis* fused tris-THF core **185** of *anti*-oxa bridge compound **176**; gold (carbon), red (oxygen), cyan (hydrogen).



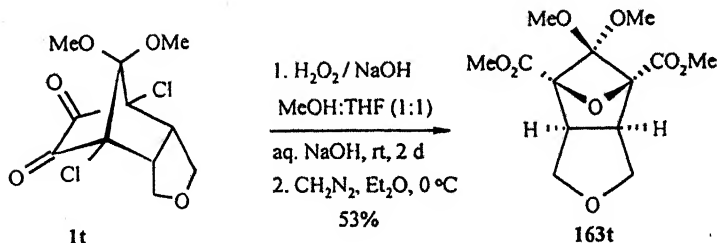
**2.4. Dioxabicyclo[3.3.0]octane core of lignans:** Natural lignans display a wide range of potent biological activities such as antitumour activity, platelet-activating factor (PAF) antagonists, and inhibitory effects on microsomal monooxygenase in insects.<sup>63</sup> The

diverse array of these potentially useful characteristics make them attractive targets for synthesis.<sup>64</sup> The 2,6-diaryl-3,7-dioxabicyclo[3.3.0]octanes (Chart 12) constitute one of the largest groups of lignans and comprise a large group of natural products exhibiting biological activities.<sup>64</sup> Fused bis-ethers of type A were found as constituents in the Chinese drug 'shin-i' and in Nigerian bark extracts. The presence of a bis-THF rings in naturally occurring lignans (Chart 12) encouraged us to successfully transform one of our easily accessible starting materials, the oxa diketone **1t** to the corresponding oxygen-bridge compound **163t** (Scheme 76). Once again the one pot transformation of using alkaline  $\text{H}_2\text{O}_2$  condition gave the optimal result. The tricyclic compound **163t** was obtained in 53% of yield, which possesses the dioxabicyclo[3.3.0]octane core of naturally occurring lignans. The highly symmetric structure of **163t** was evident from the 8 line  $^{13}\text{C}$  NMR spectrum. As seen in other oxa-bridged derivatives **163i-l**, the compound **163t** exhibited three singlets (one for two methyl esters and two for OMe groups), and the two methine and the four methylene protons showed multiplets at 3.96-3.93 and 3.54-3.47 ppm respectively in  $^1\text{H}$  NMR spectrum.

**Chart 12:** Naturally Occuring 2,6 diaryl-3,7-dioxabicyclo [3.3.0] octane Lignans

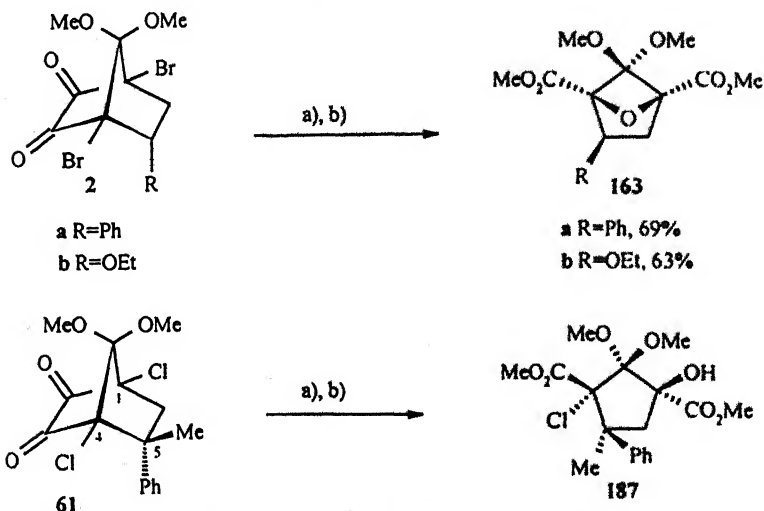


**Scheme 76:** A novel tricycle **163t** containing a *cis* bis-tetrahydrofuran core



**2.5. Bridged oxetane derivatives from mono substituted  $\alpha$ -diketones:** Further, the methodology was not restricted to only norbornyl  $\alpha$ -diketones derived from cyclic dienophiles, but the bridged oxetane derivatives with any substituent pattern could be prepared. The one-pot procedure was extended to monosubstituted  $\alpha$ -diketones **2a,b** both of which furnished the oxa-bridged products **163a,b** (Scheme 77). The only limitation appears to be for compounds with steric encumbrance in the  $\alpha$ -position (C-5), for example the dione **61**, failed to furnish the oxa-bridged derivative. The reaction stopped at  $\alpha$ -hydroxy ester stage, resulting in five membered carbocycle **187** with  $\alpha$ -hydroxy ester and  $\alpha$ -halo ester with well-defined stereochemistry (Scheme 77). The  $\alpha$ -hydroxy ester intermediate **164** was also isolated and characterized in case of **1j** by giving shorter reaction time (Scheme 66).

**Scheme 77:** One pot synthesis of oxa-bridged compound **163** and  $\alpha$ -hydroxy ester **187**



a R=Ph  
b R=OEt

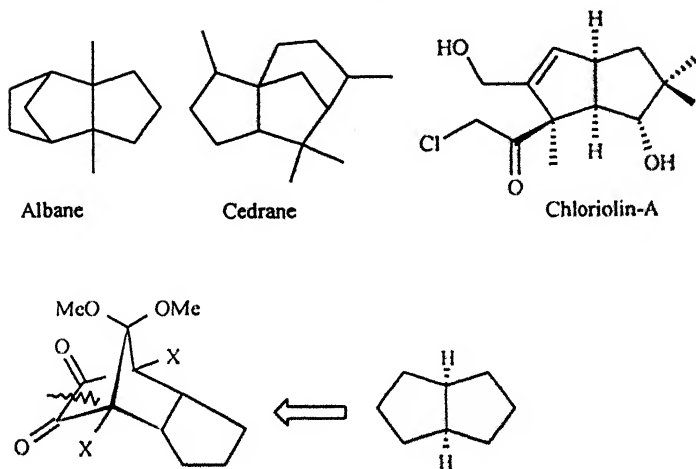
a R=Ph, 69%  
b R=OEt, 63%

Reagents and conditions: a) 30%  $\text{H}_2\text{O}_2$ /6N NaOH, MeOH, rt, 2 h, aq. NaOH, reflux, 3h, b)  $\text{CH}_2\text{N}_2$ , 0  $^\circ\text{C}$ ,  $\text{Et}_2\text{O}$ -MeOH (1:1).

**2.6. Synthesis of bicyclo[3.3.0]octanes:** The synthetic design of linearly fused polyquinanes, not surprisingly stimulated a great deal of contemporary interests due to their wide spread occurrence in nature.<sup>65</sup> The presence of diquinane skeleton as part of substructures found in terpenes (Chart 13) and also in unnatural products, prompted us to seek a direct access to these from the abundantly available tetrahalonorbornyl derivatives, utilizing our methodology. The flexibility offered by the tetrahalonorbornene derivatives to select the desired *endo* substituent allows one to design the synthesis of diverse molecules. As norbornyl  $\alpha$ -diketones serve as convenient precursors for substituted cyclopentane ring via sigma bond cleavage

between the two carbons, fused bicyclic ring systems could be easily prepared by employing a cyclic dienophile in the Diels-Alder reaction leading to norbornyls (Chart 13).

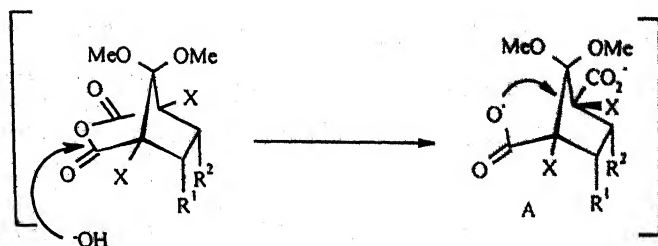
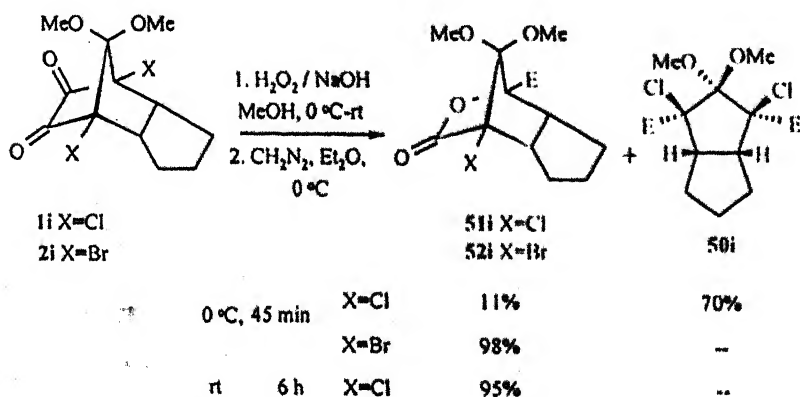
**Chart 13:** Natural products containing bicyclo [3.3.0] octane core

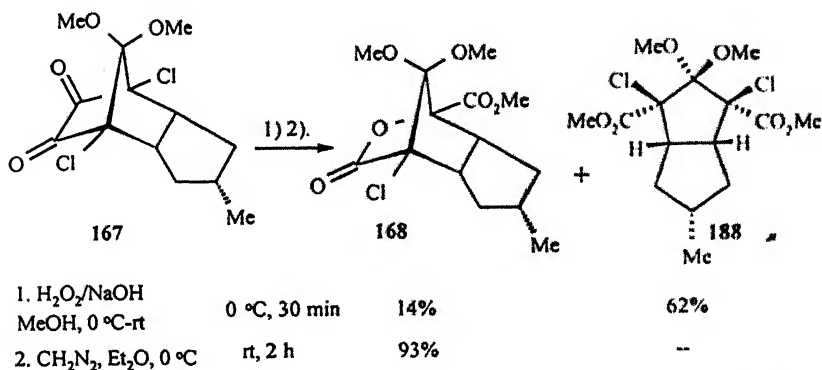


Indeed when the chloro diketone **1i** was subjected under alkaline  $\text{H}_2\text{O}_2$  mediated cleavage at  $0^\circ\text{C}$ , the diquinane derivative **50i** was formed in 70% of yield along with 11% of the tricyclic lactone **51i** (Scheme 78). At room temperature, the tricyclic lactone **51i** was exclusively formed in 95% of yield. However, the bromo analogue **2i** even at  $0^\circ\text{C}$  furnished only the tricyclic lactone **52i** in excellent yield (Scheme 78). The details were discussed in Chapter 1. Similarly the diketone **167** was transformed to tricyclic lactone **168** at room temperature while the symmetrical diquinane **188** was obtained at  $0^\circ\text{C}$  (Scheme 79).

The carboxylate groups in **A**, perhaps experiences severe steric congestion (as evident from models) with the adjacent substituents, which are in *cis* relation. This effect appears to be more pronounced in case of disubstituted derivatives (bridgehead chloro or bromo). Therefore the carboxylate group displaces one of the bridgehead halide in an  $S_N2$  fashion leading to bicyclic lactone formation with greater ease in comparison to monosubstituted cases (Scheme 78).

Scheme 78: Preparation of diquinane derivative **50i**



Scheme 79: Preparation of a functionalized diquinane derivative **188**

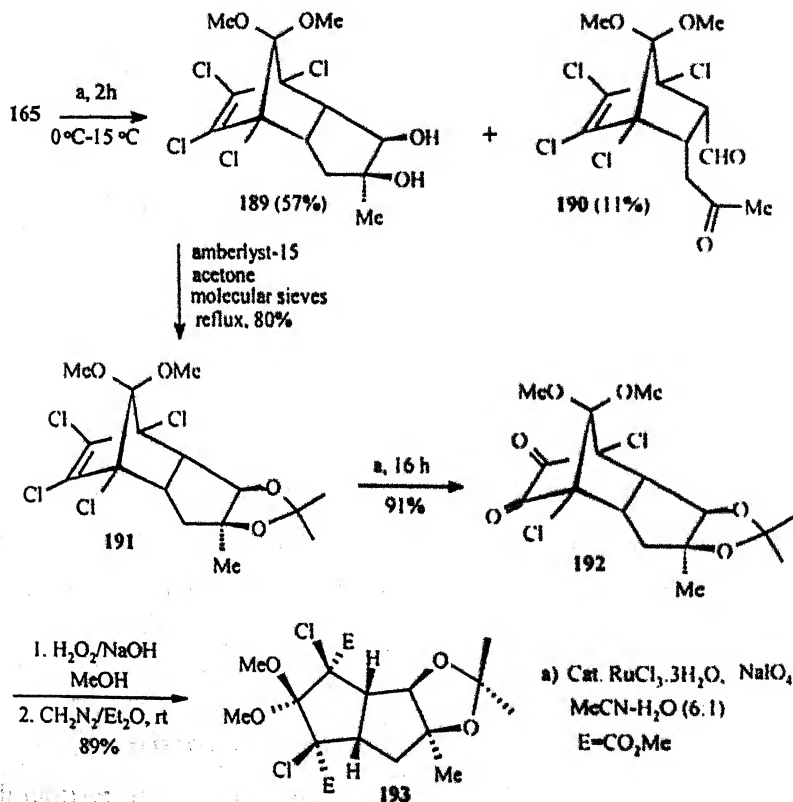
Having prepared the methylocyclopentadiene adduct **165**, we studied the ruthenium tetroxide oxidation where an additional double bond (trisubstituted) is present in *endo*-5-membered ring. The trisubstituted double bond reacts faster and the diol **189** was isolated in 57% yield along with 11% of the compound **190**, which resulted from the  $\text{NaIO}_4$  cleavage of diol **189** under the reaction condition. The product **190** is otherwise difficult to access. The diol **189** was protected as acetonide derivative **191** using acetone in amberlyst-15 in 80% yield. A highly functionalized bicyclo [3.3.0] octane derivative, **193** was conveniently achieved via the diketone **192** using the usual procedure (Scheme 80).

**2.7 Synthesis of a bicyclo[5.3.0]decane derivative:** When we performed the cleavage reaction of  $\alpha$ -diketone **1k** derived from the cycloheptene adduct at 0 °C to reveal the important hydroazulene ring system **50k**, we recorded an interesting observation. The



intermediate anhydride **194** was isolated in 77% yield along with 10% of bicyclo[5.3.0]decane derivative **50k**. A 10-line  $^{13}\text{C}$  NMR is indicative of the symmetrical nature of anhydride **194**. The carbonyl group appeared at 161.6 ppm. The IR spectrum clearly showed anhydride stretchings at 1820 and 1760  $\text{cm}^{-1}$ .

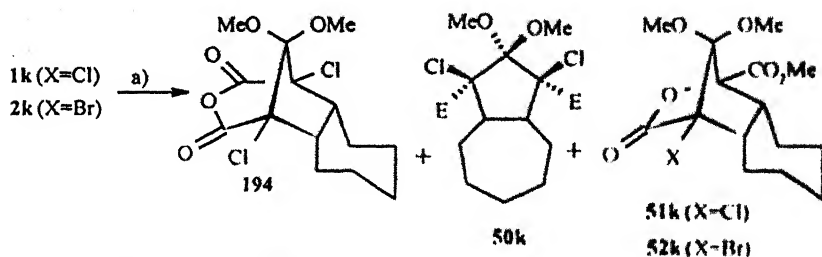
Scheme 80: Synthesis of a highly functionalized bicyclo [3.3.0] octane derivative **193**



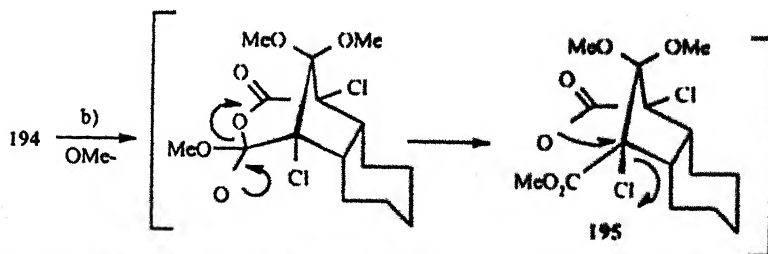
The structure of the tricyclic anhydride **194** was chemically proved by separately treating with excess (3 equiv) of NaOH in

MeOH at low temperature 0-5 °C (till the completion of the anhydride as per tlc). The caboxylate intermediate **195** acquired via opening **194** with methoxide anion furnished 12% of the lactone **51k** via intramolecular  $S_N2$  displacement of bridgehead halogen. The carboxylic acid from **195** upon treatment with diazomethane afforded the hydroazulene ring system **50k** in 71% yield (Scheme 81).

Scheme 81: Preparation of [5.5.0] decane ring system **50k**

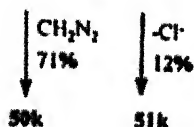


X=Cl	0 °C, 30 min	77%	10%	—
	rt, 6 h	—	—	91%
X=Br	0 °C, 1h	—	—	97%



a) 1.  $\text{H}_2\text{O}_2/\text{NaOH}$ , MeOH, 2.  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}$ , 0 °C

b) 1. 3 eq. NaOH, MeOH, 1 h, 0 °C, 2.  $\text{CH}_2\text{N}_2$ , 0 °C



A 10-line  $^{13}\text{C}$  NMR indicates the symmetrical nature of 50k. The chloroester bearing carbon appeared as a single peak at 78.5 ppm. The lactone 52k was the sole product acquired from the bromo diketone 2k, while carrying out the reaction at room temperature for 6 h, the chloro analogue 1k also furnished exclusively the bridged lactone 51k.

### 3. Conclusion

One pot transformation of  $\alpha$ -diketones to oxabridge derivatives was achieved and generalized by transforming a variety of norbornyl  $\alpha$ -diketones to the corresponding strained oxa-bridged compounds. A novel and stereoselective strategy for the replacement of 1,2-dihaloalkene-bridge of tetrahalonorbornyl derivatives by an oxygen bridge is developed. The *endo*, *anti*, *endo* 2:1 bis adducts of tetrachloro dimethoxy cyclopentadiene with cyclopentadiene and furan could serve as perspective building blocks for *cis:anti:cis* triquinanes and oxatriquinanes.

## Chapter 3A

### Regio- and Diastereoselective Reduction of Non-enolizable $\alpha$ -Diketones to Acyloins Mediated by Indium Metal

#### 1. Introduction

The acyloin ( $\alpha$ -hydroxyketone) functional group plays an important role in organic synthesis, and is widespread in compounds of natural origin as well as in advanced intermediates enroute to several target molecules.<sup>66</sup> Conventionally,  $\alpha$ -hydroxyketones are prepared by acyloin condensation reaction,<sup>67</sup> oxidation of enolates,<sup>68</sup> and reduction of  $\alpha$ -diketones<sup>69</sup> using  $\text{VCl}_2$ ,<sup>69a</sup> zinc,<sup>69b</sup>  $\text{NaHSi}$ ,<sup>69c</sup> titanocene,<sup>69d</sup>  $\text{BINAP-Ru (II)}$  complexes,<sup>69e</sup>  $\text{Ti(III)}$ ,<sup>69f</sup>  $\text{TiI}_4$ .<sup>69g</sup> However, the problems of over-reduction to a diol<sup>70</sup> or to an  $\alpha$ -methylene ketone<sup>71</sup> that are associated with reduction of  $\alpha$ -diketones makes this procedure less attractive. Thallium (III) promoted  $\alpha$ -oxidation of ketones to  $\alpha$ -acetoxy ketones is the most recent entry to the growing list.<sup>72</sup>

In continuation of our ongoing research program, we became interested in norbornyl-based acyloins possessing bridgehead halogens. It occurred to us that the corresponding  $\alpha$ -diketones could be suitable precursors, provided an efficient and selective method could be developed. We focused our attention on indium metal as a potential reducing agent.<sup>73</sup> Indium-mediated reactions have gained considerable importance in the recent past due to their mild nature, functional group tolerance, high stereoselectivity, ease of handling and versatility of the

reagent for a number of useful transformations that could be carried out even in water as solvent, without a need to rigorously exclude air.<sup>74</sup> However, although indium has been widely used in synthetically useful carbonyl addition reactions,<sup>74</sup> but there are limited number of reports in the literature on indium mediated reductions.<sup>73</sup>

The reducing power of indium is lower than that of other popular reducing agents used in organometallic reactions like tin, chromium (II), aluminium and magnesium (Chart 14). However its first ionization potential (I.P.) is close to that of alkali metals such as sodium or lithium and much lower than zinc, magnesium or tin (Chart 14). In addition, unlike alkali metals, indium is not sensitive to boiling water or alkali and does not form oxides readily in air. Since the ionization potential is directly associated with the capability of the metal to release electrons, the indium mediated reactions apparently proceed by a single electron transfer (SET) mechanism.

**Chart 14:** The reducing power and first ionization potential of some metals<sup>75</sup>

**The reducing power of In < Sn, Cr, Mg, Al, Zn**

$$E^0 (\text{In}^{3+} / \text{In}^0) = -0.34 \text{ v}$$

$$E^0 (\text{Sn}^{2+} / \text{Sn}^0) = -1.38 \text{ v}$$

$$E^0 (\text{Mg}^{2+} / \text{Mg}^0) = -2.37 \text{ v}$$

$$E^0 (\text{Zn}^{2+} / \text{Zn}^0) = -0.76 \text{ v}$$

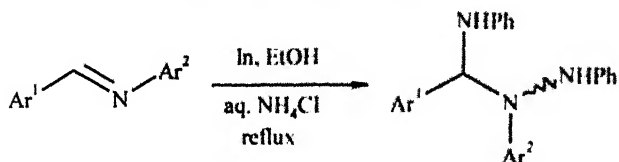
**The first I.P. of In (5.79 ev) < Zn (9.39 ev), Mg (7.65 ev),**

**Sn (7.43ev), Al (5.98 ev), Ga, Th,**

**$\approx$  Li (5.39), Na (5.1 ev)**

Indium metal as a reducing agent was first reported by Kalyanam.<sup>76</sup> They established the reductive coupling of imines to give 1,2-diamines by using indium metal in ethanolic aqueous ammonium chloride (Scheme 82). However the reaction was selective for the coupling of aldimines derived from aromatic aldehydes and aromatic amines.

Scheme 82: Aza-Pinacol Coupling reaction mediated by indium<sup>76</sup>



Ar<sup>1</sup>, Ar<sup>2</sup> = Ph, 4Me-Ph, 4OMe-Ph, 2OMe-Ph, 2Cl-Ph

Since then indium metal has been used as a mild and potential reducing agent for a number of useful transformations.<sup>77-82</sup> some of the examples are summarized in Chart 15 and Chart 16. The indium mediated reductions were extensively studied by Ranu<sup>73a,77</sup> and Moody.<sup>73b,78</sup> Ranu successfully utilized indium metal in the stereoselective reductive elimination of 1,2 dibromides to *trans*-alkenes,<sup>77a</sup> reduction of aryl-substituted *gem*-dibromides to vinyl bromides,<sup>77b</sup> reduction of terminal alkynes to alkenes,<sup>77c</sup> and reductive homocoupling of aryl and alkyl iodides to the corresponding dialkyls and biaryls<sup>77d</sup> (Chart 15). The indium mediated selective reduction of the heterocyclic rings in quinolines, quinoxalines,<sup>78a</sup> aromatic nitro groups,<sup>78b</sup> the reductive acetylation of oximes,<sup>78c</sup> were efficiently achieved by Moody and coworkers (Chart 16). Indium metal is also

effectively used for the reduction of conjugated alkenes<sup>73a</sup> (Chart 15), the pinacol coupling reactions (Chart 16),<sup>79</sup> reduction of N-oxides<sup>80</sup> and azides (Chart 16).<sup>81</sup> In mediated reductive dehalogenation of  $\alpha$ -halocarbonyl compounds,<sup>77e</sup> the reductive coupling of acyl cyanides,<sup>82</sup> etc. were also reported.

Chart 15: Indium mediated reductions<sup>73, 77, 79</sup>

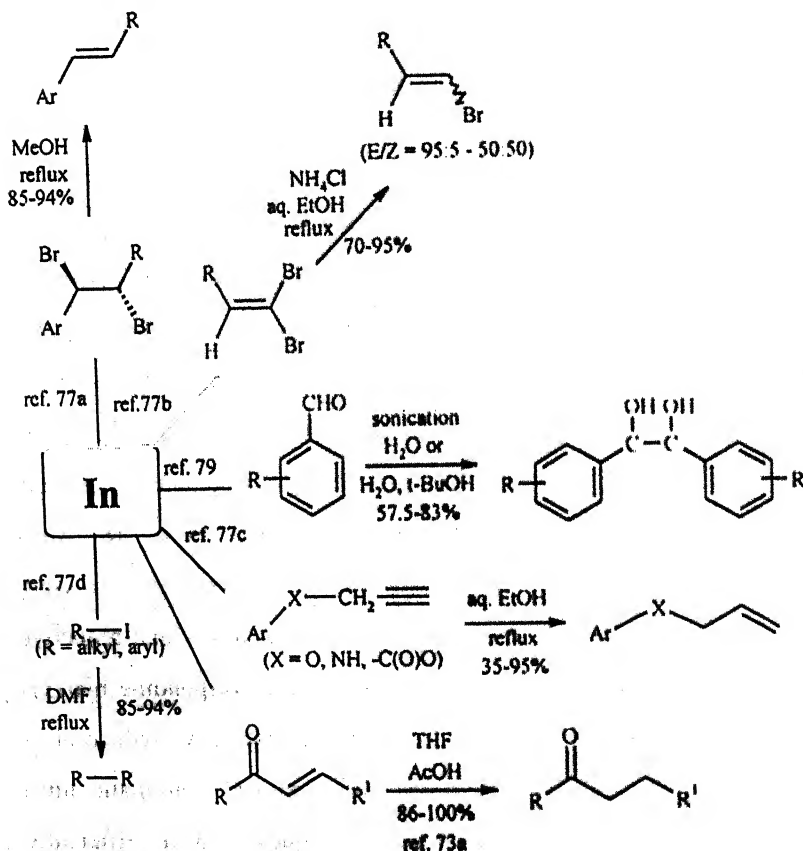
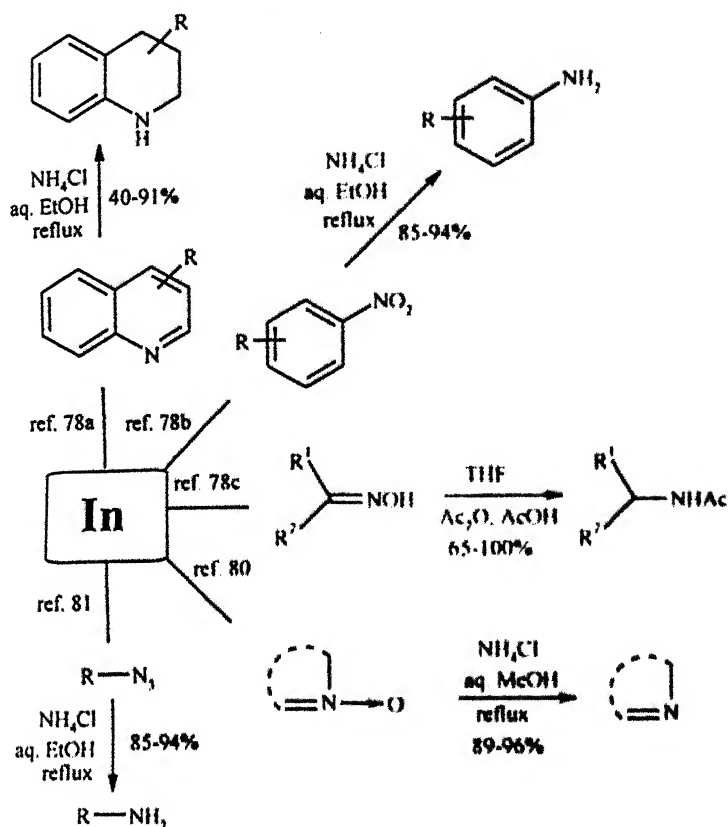


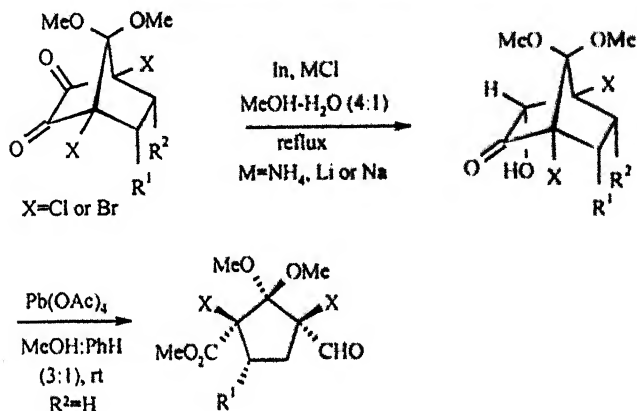
Chart 16: Indium mediated reductions<sup>78,80,81</sup>

In continuation of our work on indium mediated reactions,<sup>81</sup> this section presents a mild, efficient and stereoselective route to acyloins by indium mediated reduction of non-enolizable  $\alpha$ -diketones.<sup>14</sup>  $\alpha$ -Diketones are efficiently reduced with indium metal in methanol-water in the presence of  $\text{NH}_4\text{Cl}$ ,  $\text{LiCl}$  or  $\text{NaCl}$  to give regio- and diastereoselectively the corresponding acyloins in good to excellent yield. The cleavage of the acyloins under  $\text{Pb}(\text{OAc})_4/\text{MeOH-PhH}$



condition provides a convenient and regioselective access to highly functionalized cyclopentane carboxaldehydes, potential building blocks in organic syntheses (Scheme 83).<sup>14</sup>

Scheme 83: Indium mediated reduction of norbornyl  $\alpha$ -diketones<sup>14</sup>

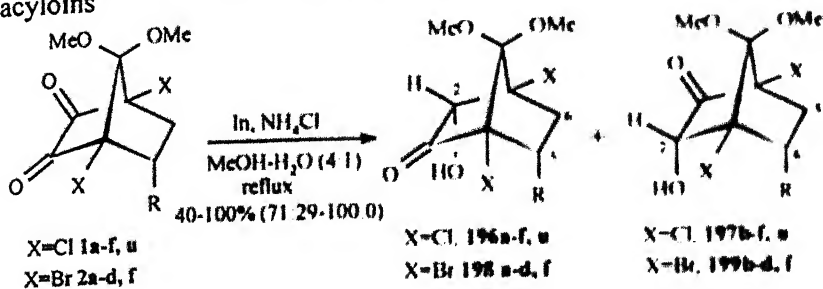


## 2. Results and Discussion

The reduction of  $\alpha$ -diketones were carried out using indium metal (cut into small pieces, before use) in MeOH:H<sub>2</sub>O (4:1) at reflux temperature in the presence of either  $NH_4Cl$ ,  $LiCl$  or  $NaCl$  (Tables-2, 3, 5). Both chloro and bromo derivatives underwent smooth transformation to the corresponding acyloins in a regio- and stereoselective manner.

**2.1 Reduction of Mono Substituted  $\alpha$ -Diketones:** We first examined the mono substituted derivatives 1,2a-f. The results obtained with aqueous MeOH and  $NH_4Cl$  are summarized in Table 2.

**Table 2.** Indium mediated reduction of monosubstituted  $\alpha$ -diketones to acyloins<sup>a</sup>



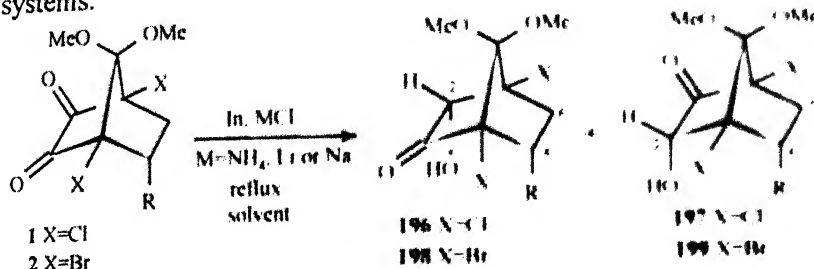
Entry	Substrate	R	Time (h)	Yield (%) <sup>b</sup>	Product Ratio <sup>c</sup> 196:197 for 1 198:199 for 2
1	<b>1a</b>	Ph	12	97	100:0
2	<b>1b</b>	OEt	12	100	71:29
3	<b>1c</b>	CH <sub>2</sub> OAc	4	84	93:7
4	<b>1d</b>	OAc	12	68	100:0
5	<b>1e</b>	SiMe <sub>3</sub>	7	96	81:19
6	<b>1f</b>	CO <sub>2</sub> Me	6	76 <sup>d</sup>	65:35
7	<b>1u</b>	CH <sub>2</sub> OMe	9	99	80:20
8	<b>2a</b>	Ph	4	52	100:0
9	<b>2b</b>	OEt	9	83	81:19
10	<b>2c</b>	CH <sub>2</sub> OAc	12	34	85:15
11	<b>2d</b>	OAc	6	40	100:0
12	<b>2f</b>	CO <sub>2</sub> Me	10	68 <sup>e</sup>	68:32

<sup>a</sup> All reactions were run using 2 eq. Indium metal. <sup>b</sup> Isolated yields of analytically pure b+c. <sup>c</sup> THF:H<sub>2</sub>O (4:1) was used. <sup>d</sup> For X=Cl, 196:197, For X=Br, 198:199

The  $\alpha$ -diones **1a-f,u** and **2a-d,f** were efficiently reduced to furnish **196a-f,u** and **198a-d,f** as the major, and **197b-f,u**, **199b-d,f** as the minor *endo* alcohols (Table 2). Although mechanistically both the carbonyl groups are simultaneously involved in electron transfer process, formally it appears as though the reduction of the carbonyl group was taking place exclusively from the *exo* face of the diketones **1,2** either to the diagonal or same side of the *endo* substituents. The major alcohols, **196a-f,u** and **198a-d,f** were derived from the (formal) reduction of the diagonal carbonyl group, while the other carbonyl group was reduced to furnish the minor *endo* alcohols **197b-f,u**, **199b-d,f**. The reaction was highly stereoselective leading to *endo* alcohols, and the regioselectivity varied from 70:30 to 100:0 for the two isomeric alcohols in high yield (Table 2). The product distribution of alcohols **196,198** and **197,199** was determined by  $^1\text{H}$  NMR integration at 400 MHz of the crude reaction mixture before column purification (in most of the cases); and in some cases a short silica gel column filtration was conducted.

The diketones **1a** and **2a** having *endo* phenyl substituent furnished essentially a single regioisomer **196a** and **198a** respectively (entries 1 and 8, Table 1). The yields were generally high in aqueous MeOH except in case of substrates **1,2 d** (*endo* OAc derivatives), **2c** *endo*  $\text{CH}_2\text{OAc}$  derivatives (entries 4, 10 and 11, Table 2). We studied the reactions under different solvent systems and using different additives (Table 3, comparison between aqueous MeOH and THF is particularly interesting).

**Table 3:** Comparison of yield and regioselectivity in different solvent systems.



Entry	Substrate	Solvent:H <sub>2</sub> O (4:1)	Additive	Time (h)	Yield (%) <sup>b</sup>	Product Ratio <sup>c</sup>
1			--	14	96	100:0
2		MeOH-H <sub>2</sub> O	NH <sub>4</sub> Cl	12	97	100:0
3	<b>1a</b>		NaCl	12	95	100:0
4		MeOH-10%HCl	--	13	95	100:0
5		MeOH	--	40	No reaction	
6	<b>1b</b>	THF	NH <sub>4</sub> Cl	23	No reaction	
7	<b>1c</b>	MeOH-H <sub>2</sub> O	NH <sub>4</sub> Cl	4	84	93:7
8		THF-H <sub>2</sub> O		15	96	64:36
9	<b>1d</b>	MeOH-H <sub>2</sub> O	NH <sub>4</sub> Cl	12	68	100:0
10		THF-H <sub>2</sub> O	LiCl	16	90	70:30
11		MeOH-H <sub>2</sub> O	MCl <sup>e</sup>	6	~30% crude	
12	<b>1f</b>	THF-H <sub>2</sub> O	NH <sub>4</sub> Cl	11	96 <sup>d</sup>	51:49
13		THF-H <sub>2</sub> O	NH <sub>4</sub> Cl	6	76	65:35
14	<b>2a</b>	MeOH-H <sub>2</sub> O	NH <sub>4</sub> Cl	4	52	100:0
15		THF-H <sub>2</sub> O	NH <sub>4</sub> Cl	16	91	100:0
16	<b>2c</b>	MeOH-H <sub>2</sub> O	NH <sub>4</sub> Cl	12	34	85:15
17		THF-H <sub>2</sub> O	NH <sub>4</sub> Cl	5	68	85:15
18	<b>2d</b>	MeOH-H <sub>2</sub> O	NH <sub>4</sub> Cl	6	40	100:0
19		THF-H <sub>2</sub> O	LiCl	6	85	80:20

<sup>a</sup> All reactions were run using 2 eq. Indium metal. <sup>b</sup> Isolated yields of analytically pure b+c. <sup>c</sup> MCl (NH<sub>4</sub>Cl or LiCl). <sup>d</sup> slow addition of the substrate to the reagent. <sup>e</sup> For 1 X=Cl, 196:197, For 2 X=Br, 198:199

The reactions performed in MeOH-H<sub>2</sub>O (4:1) proceed faster than THF-H<sub>2</sub>O (4:1). The reaction was sluggish with anhydrous THF or MeOH (entries 5, 6). The presence of an additive MCl (NH<sub>4</sub>Cl, LiCl or NaCl) was not essential for the reaction (entry 1, 11), but it was found to accelerate the rate of the reaction. The reaction was also performed with MeOH and 10% HCl for the substrate **1a** (entry 4, Table 3) to give the desired product **196a** in high yield.

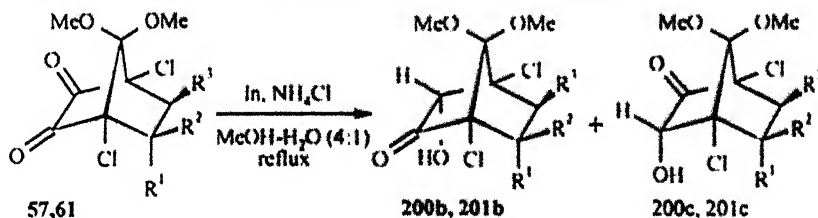
By changing the solvent system to THF-H<sub>2</sub>O (4:1), the yields were considerably improved in cases where aqueous MeOH gave poor results (entries 7-19). However, for the substrates **1c**, **1d** and **2d**, the use of aqueous THF enhanced the yield of the reaction; albeit at the expense of diminished regioselectivity (compare entries 7-8, 9-10, 18-19). In case of *endo* OAc derivative **1d**, only one regioisomer (from crude <sup>1</sup>H NMR of the product) was formed in 68% of yield using MeOH as solvent (entry 9), while performing the reaction in aq. THF afford a 70:30 mixture of acyloins **196a** and **197a** in 90% of yield (entry 10).

In aqueous methanolic medium the products could not be isolated from substrate **1f** (a long streak on TLC and very poor yield of the crude product ~30%, entry 11), while the reaction underwent smoothly in THF-H<sub>2</sub>O showing moderate regioselectivity (entry 13), and a near quantitative yield was obtained by slow addition of the substrate but the regioselectivity dropped to 1.04:1 (entry 12). Therefore aqueous THF was preferred with other ester substrates **2f**, **1m**, **57** and **205**. The solvent system 4:1 THF-H<sub>2</sub>O gave satisfactory

results in case of ester derivatives **1f**, **2f** and **1m**; which reacted sluggishly in aqueous methanolic medium. The two solvent systems appear to play an important role with respect to the yield and regioselectivity of the products. In MeOH-H<sub>2</sub>O, the regioselectivity is high compared to aqueous THF, but for sensitive substrates the later gives better result in terms of yield. This suggests the product distribution of two acyloins **196**, **198** and **197**, **199** is probably due to the protonation of the common acyloinate intermediate.

The derivatives **57** and **61** follow the same trend as the monosubstituted cases (Scheme 84) demonstrating that an additional *exo* substituent placed either on the vicinal carbon or on the same carbon that bears the *endo* substituent has no influence on the regio- and diastereoselectivity (compare entries 1 and 6, Table I).

**Scheme 84:** Indium mediated reduction of diketones having *exo* substituents



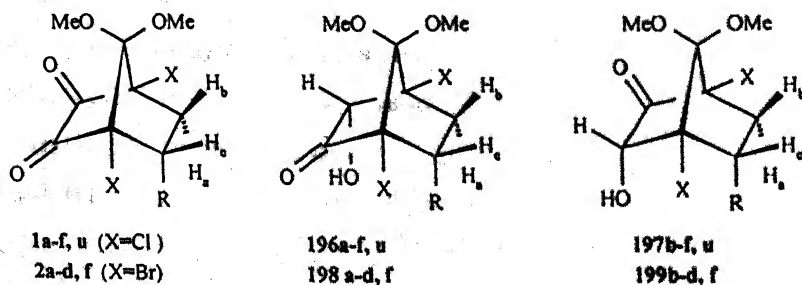
Substrate	R <sup>1</sup>	R <sup>2</sup>	R <sup>3</sup>	Products	Time	Yield(%)	Ratio
<b>57</b>	CO <sub>2</sub> Me	H	Me	<b>200b,c</b>	7h 10h	75 87 <sup>a</sup>	67 : 33 54 : 46
<b>61</b>	Ph	Me	H	<b>201b</b>	9h	95	100 : 0

<sup>a</sup> THF-H<sub>2</sub>O (4:1) is used as solvent with LiCl.

The structural assignments in case of the products derived from the mono substituted derivatives were made from their  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra. It is known that in bicyclo [2.2.1] systems the presence of an *endo* oxygen substituent at  $\text{C}_2$  has a remarkable deshielding effect on the *endo*- $\text{H}_6$ . The *exo*- $\text{H}_6$  also experiences a shielding effect.

The comparison of  $^1\text{H}$  NMR (400 MHz) values of *exo* and *endo*- $\text{H}_6$  of acyloins with those of the parent  $\alpha$ -diketone unambiguously confirms the stereochemical assignments (Table 4). In compounds 196 and 198 the *endo*- $\text{H}_6$  clearly showed consistent deshielding effect ranging from 0.2 to 0.5 ppm while the *exo*- $\text{H}_6$  is shielded by 0.2 to 0.4 ppm (Table 4). No such effect was observed with minor alcohols 197 and 199 (Table 4). The spin decoupling experiment was carried out to unambiguously assign the *endo*- $\text{H}_6$  and *exo*- $\text{H}_6$  protons and to find out the W-couplings in some of the cases (see experimental section).

**Table 4:** Comparison of 400 MHZ  $^1\text{H}$  NMR chemical shift values in ppm for  $\text{H}_a$ ,  $\text{H}_b$  and  $\text{H}_c$  in monosubstituted diketones and the corresponding acyloins



Diketone	H <sub>a</sub>	H <sub>b</sub>	H <sub>c</sub>	acyloin	H <sub>a</sub>	H <sub>b</sub>	H <sub>c</sub>
1a	2.48	3.07	3.91	196a	2.92	2.67	3.74
1b	2.13	2.98	4.28	196b	2.48	2.63	4.13
				197b	1.96	2.77	4.39
1c	2.18	2.75	3.02	196c	2.46	2.40	2.88-
							2.81
				197c	1.84	2.61	3.04-
							2.96
1d	2.06	3.14	5.48	196d	2.48	2.76	5.35
				197d	1.89	2.97	5.54
1e	1.90	2.19	2.67	196e	1.96	2.25	2.38
				197e	1.75	2.03	2.47
1f	2.37	2.83	3.61-	196f	2.55	2.64	3.41
			3.68	197f	2.56	2.48	3.49
1u	2.32	2.62	2.83	196u	2.43-	3.36	2.69
				197u	2.06	2.46	2.88
2a	2.53	3.13	3.96	198a	2.98	2.76	3.78
2b	2.18	2.99	4.31	198b	2.54	2.70	4.17
				199b	2.01	2.80	4.44-
							4.41
2c	2.16	2.73	2.98	198c	2.54	2.48	2.88
				199c	1.90	2.66	3.07-
							2.99
2d	2.12	3.18	5.51	198d	2.54	2.86-	5.38
						2.80	
				199d	1.95	3.01	5.56
2f	2.40	2.89	3.64	198f	2.70	2.62	3.47
				199f	2.59-	2.56	3.56
57	2.41	1.47 <sup>a</sup>	3.27	200b	2.90	1.39 <sup>a</sup>	3.08
				200c	2.52	1.32 <sup>a</sup>	3.20
61	2.80	3.08	1.80 <sup>a</sup>	201b	3.48	2.53	1.69 <sup>a</sup>

<sup>a</sup> ppm values of (exo Me) is given



Figure 7a:  $^1\text{H}$  NMR (400 MHz) spectrum of diketone 1b

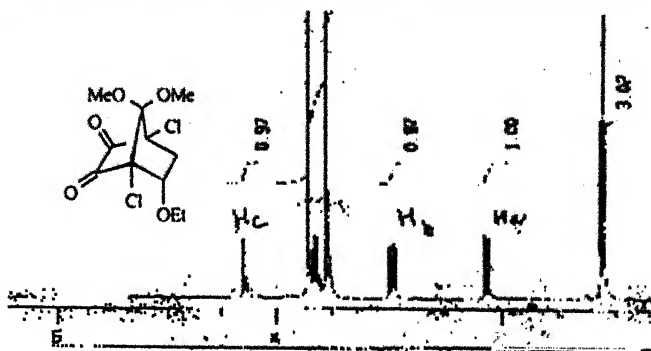


Figure 7b:  $^1\text{H}$  NMR (400 MHz) spectrum of major acyloin 196b

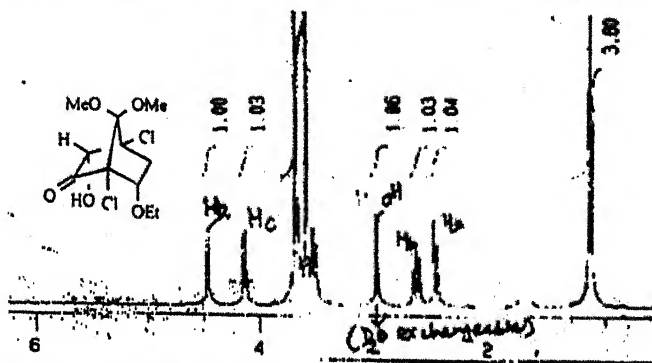


Figure 7c:  $^1\text{H}$  NMR (400 MHz) spectrum of minor acyloin 197b

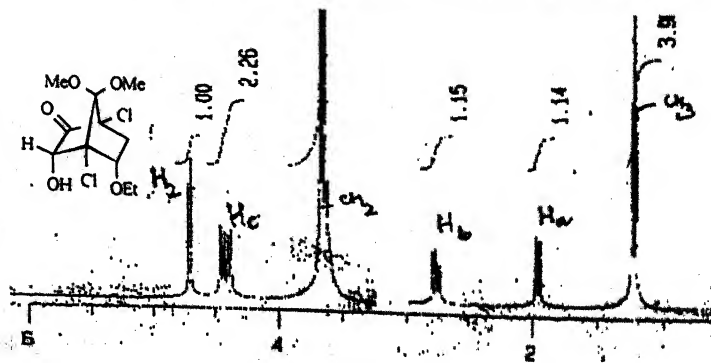
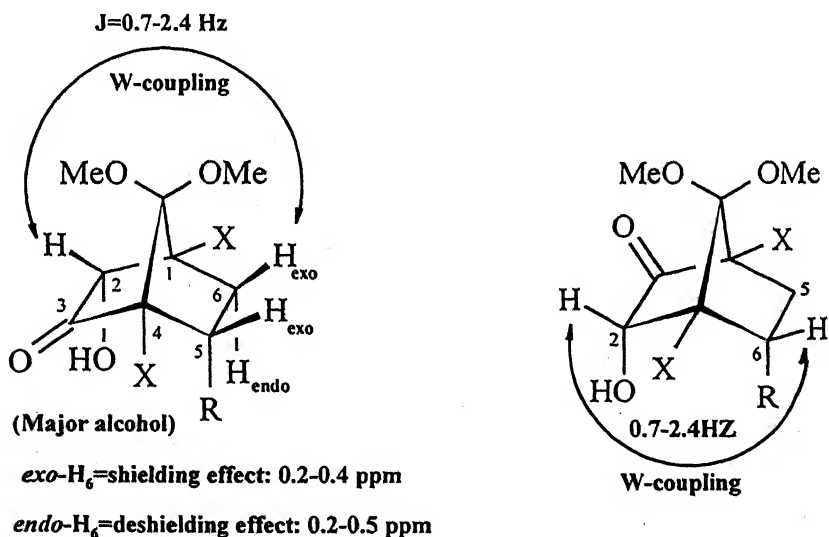


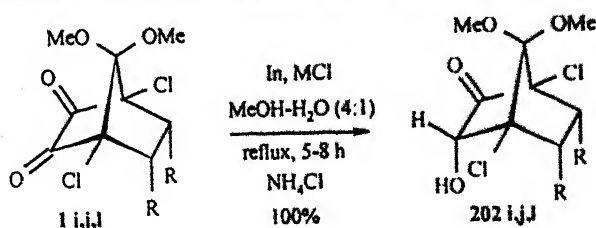
Figure 7a-c presents the 400 MHz  $^1\text{H}$  NMR spectra of the parent diketone **1b** and the major and minor  $\alpha$ -hydroxy carbonyl compounds **196b**, and **197b**; which clearly shows the deshielding of  $\text{H}_a$ , shielding of  $\text{H}_b$  in case of **196b**. The shielding and deshielding effects of the protons attached to C(5) and C(6) carbon of major and minor acyloins (the basis products were assigned) are summarized in Figure 8. Further proof for both isomers **196**, **198** and **197**, **199** came from the W-Coupling between the carbinol *exo*- $\text{H}_2$  and the *exo*- $\text{H}_6$  (0.7-2.4 Hz). In  $^{13}\text{C}$  NMR spectrum,  $\text{C}_6$  is consistently shielded by 3-4 ppm due to the presence of *endo*-OH at  $\text{C}_2$ .

**Figure 8:** The  $^1\text{H}$  NMR assignments for regioisomeric acyloins



**2.2 Reduction of disubstituted  $\alpha$ -diketones:** In case of disubstituted derivatives **1i,j** and **1l** indium mediated reduction proceeds stereoselectively to furnish the *endo* alcohols **202i,j** and **202l** in near quantitative yield (Scheme 85). In each case the characteristic W-coupling between the carbinol *exo*-H<sub>2</sub> and the *exo*-H<sub>6</sub> was observed.

Scheme 85: Indium mediated reduction of disubstituted  $\alpha$ -diketones



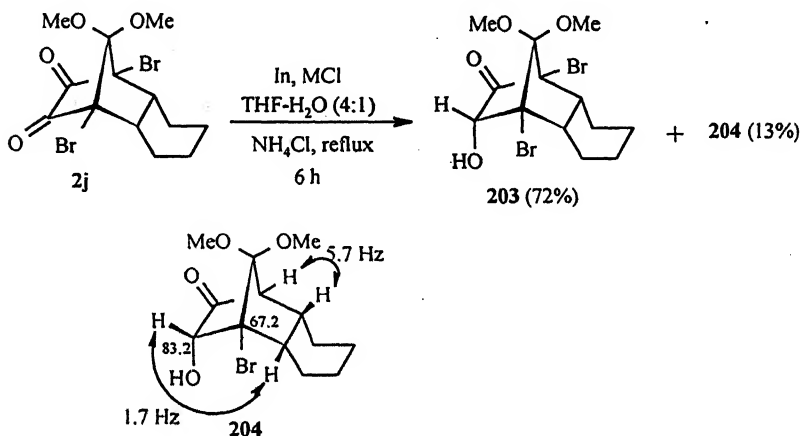
	R	Time (h)
1i	-(CH <sub>2</sub> ) <sub>3</sub> -	8
		7a
1j	-(CH <sub>2</sub> ) <sub>4</sub> -	5
1l	-(CH <sub>2</sub> ) <sub>6</sub> -	7

aNaCl was used in place of NH<sub>4</sub>Cl

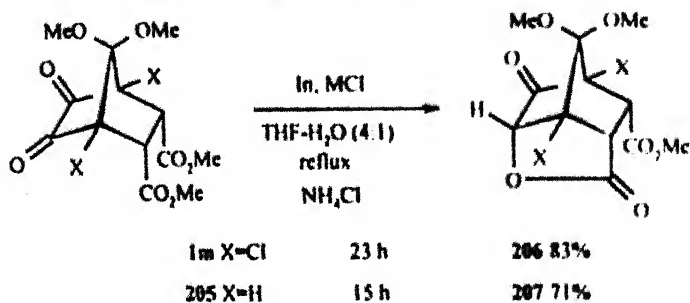
When indium reduction of the diketone **2j** was carried out, the acyloin **203** was formed in 72% of yield along with the minor product **204** in 13% of yield (Scheme 86). The product **204** was formed via over reduction of **2j**, the bromine  $\alpha$  to the carbonyl was reduced. The alcohol **204** was characterized based upon the coupling shown by the bridgehead proton with the *exo*-H<sub>5</sub> and W-coupling between the carbinol *exo*-H<sub>2</sub> and the *exo*-H<sub>6</sub> (as indicated in the structure of **204**). Further structural proof comes from the vicinal coupling constant,  $J =$

5.7 Hz between the bridgehead hydrogen and *exo*-H<sub>5</sub>. The characteristic signals for bromine bearing bridgehead and carbinol carbon at 67.2, 83.2 ppm respectively, for **204** in <sup>13</sup>C NMR spectrum unambiguously confirmed the structural assignment.

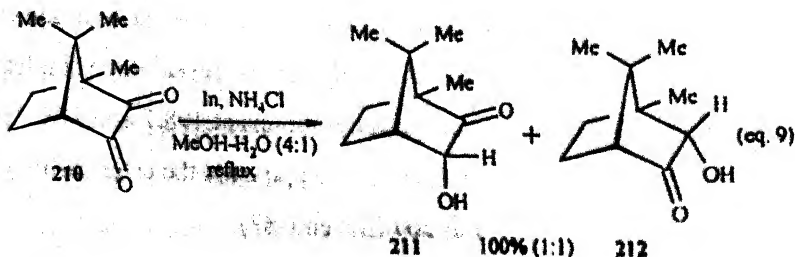
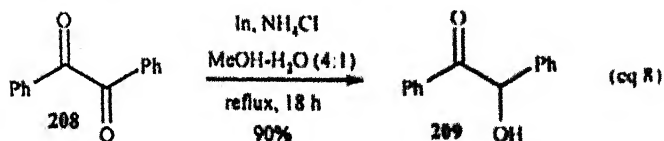
**Scheme 86:** Indium mediated reduction of disubstituted  $\alpha$ -diketone **2j**



The resulting initial *endo* alcohols, obtained from indium reduction of diester derivatives **1m** and **205** cyclized to furnish the corresponding lactones **206** and **207**. The formation of lactones, provide an additional proof for the observed exclusive *endo* diastereoselection. The <sup>1</sup>H NMR spectrum of lactones **206** and **207** reveal three singlets for OMe and <sup>13</sup>C NMR show the carbonyl groups at 198.7 and 188.8 ppm, the lactone carbonyls at 175.0 and 171.5 ppm, and the ester carbonyls at 169.5-166.9 ppm for **206** and **207** (Scheme 87).

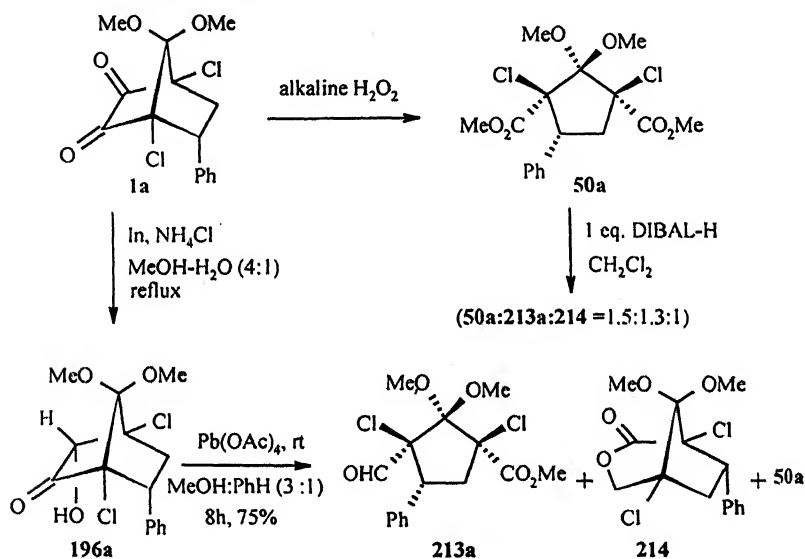
**Scheme 87:** Indium mediated reduction of diester derivatives

Further, the method was successfully employed for the smooth reduction of benzil **208** to benzoin **209** in high yield (eq. 8). The reduction of camphorquinone **210** also proceeded efficiently in quantitative yield in MeOH-H<sub>2</sub>O giving rise to 1:1 mixture of regioisomers **211** and **212** (eq. 9). The structural assignments in this case were based on the literature report.<sup>84</sup>



**2.3 Cleavage of Acyloins:** After successfully developing the methodology for the regioselective reduction of diketones, it occurred to us that the cleavage of acyloin, particularly for monosubstituted norbornyl derivatives, could be highly fruitful in achieving stereoselective transformation and may lead to derivatives that are not easily accessible otherwise.<sup>14</sup>

**Scheme 88:** Cleavage of acyloin **196a** by lead tetracetate

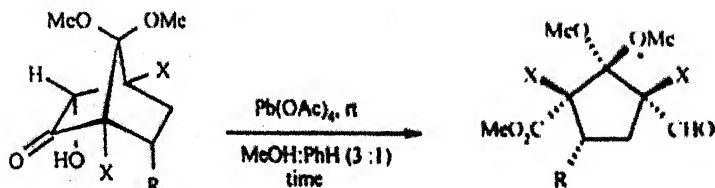


For example, the attempted selective reduction of **50a**, obtained by basic  $\text{H}_2\text{O}_2$  cleavage<sup>1</sup> of diketone **1a** (discussed in Chapter-1A), using 1 equivalent of DIBAL-H at  $-78^\circ\text{C}$  furnished a mixture (Scheme 88). The starting bis( $\alpha$ -chloro ester) cyclopentane derivative **50a**, five membered aldehyde **213a** and the bicyclic lactone **214** (obtained via reduction of the resulting aldehyde **213a**) were formed in a ratio of

1.5 : 1.3 : 1 (Scheme 88), thus disqualifying this as a useful route to aldehyde 213a. The ratio of the products 50a, 213a and 214 were determined by  $^1\text{H}$  NMR integration at 400 MHz of the unpurified reaction mixture prior to column purification.

On the other hand, the treatment of acyloin 196a, obtained via indium reduction of 1a, furnished the aldehyde 213a in good yield upon treatment with  $\text{Pb}(\text{OAc})_4$  in  $\text{MeOH-PhH}$  (3:1), thus constituting an efficient and stereoselective route to highly functionalized cyclopentane carboxaldehydes (Scheme 88). The procedure was efficiently extended to other derivatives 196b, 196d, 196e and 198b to obtain the corresponding cyclopentane carboxaldehydes in good yield (Scheme 89).

Scheme 89: Lead tetraacetate Cleavage of Acyloins<sup>14</sup>

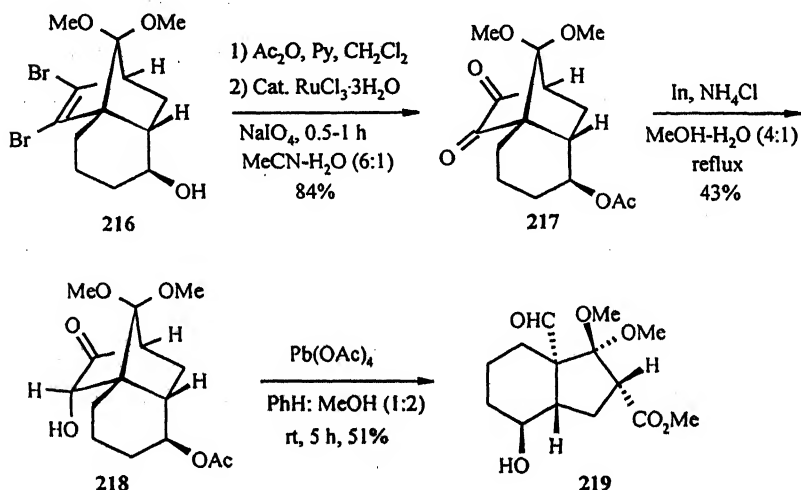


196a X=Cl, R=Ph	8h	213a 75%
196b X=Cl, R=OEt	7h	213b 77%
196d X=Cl, R=OAc	4.5h	213d 79%
196e X=Cl, R=TMS	5h	213e 71%
198b X=Br, R=OEt	6h	215b 78%

We wanted to make use of this strategy in an ongoing project towards the synthesis of *trans*-hydrindane derivative present in biologically active naturally occurring molecules.<sup>28</sup> The methodology

was efficiently used to selectively incorporate the angular aldehyde group in the *trans*-hydrindane derivative **219** (Scheme 90). This is in order to circumvent the difficulty encountered when the diketone derived from **216** was directly cleaved to give the diester,<sup>28</sup> where there is no possibility for selective transformation as both groups were same.

**Scheme 90:** Synthesis of a *trans*-hydrindane derivative



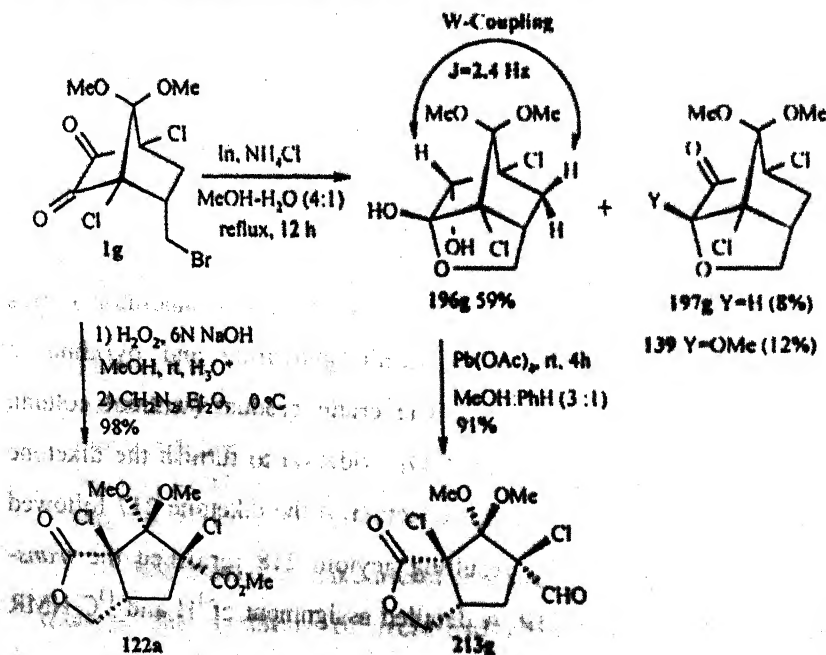
The alcohol **216** (prepared earlier in our laboratory), was protected as acetate by using acetic anhydride and pyridine in dichloromethane (Scheme 90). The crude product (without column purification) was subjected to  $\text{RuO}_4$  oxidation to furnish the diketone **217** in 84% yield. The indium reduction of the diketone **217** followed by LTA cleavage of the resulting acyloin **218** furnished the *trans*-hydrindane derivative **219**. A detailed assignment of  $^1\text{H}$  and  $^{13}\text{C}$  NMR



values for 218 and 219 is presented in the experimental section (Page no. 274).

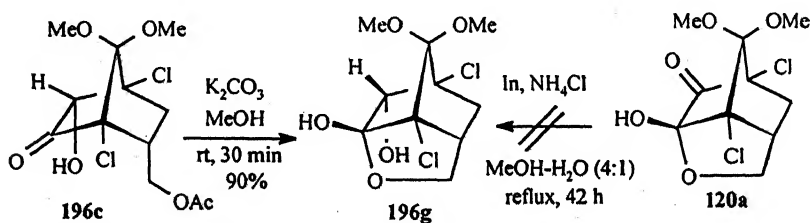
A direct alkaline cleavage of allyl bromide as dienophile, derived diketone 1g gave the  $\gamma$ -lactone derivative 122a having  $\alpha$ -haloester substituent (discussed in Chapter 1C, page no. 64). While distinguishing the two reducible moiety of the lactone derivative 122a was not possible, but if the reaction was carried out after indium mediated reduction of 1g, lead to a compound 213g, having groups distinctively different in reactivity towards hydride based reducing agents providing a handle for selective transformation (Scheme 91).

Scheme 91: Preparation of a functionalized  $\gamma$ -lactone



When the diketone having *endo* bromo methyl substituted derivative **1g** was subjected to indium mediated reduction, three products **196g**, **197g** and **139** were isolated (Scheme 91). The reduction was taking place first followed by the intramolecular displacement leading to the diol **196g** as the major product in 59% yield, where the carbonyl group diagonal to the *endo* substituent was (formally) reduced. The minor product **197g** was isolated in 8% yield. However, a competing reaction of intramolecular nucleophilic displacement of bromine was observed under the reaction condition leading to the formation of trimethoxy oxa-tricyclo ketone, **139** (the formation of which by different routes was detailed in Chapter 1C). The diol was characterized from 400 MHz  $^1\text{H}$  NMR spectral data based on W-coupling ( $J = 2.4$  Hz) shown by carbinol hydrogen at  $\text{C}_2$  with the *exo* proton as indicated on **196g** (Scheme 91). Further, chemical proof for the structure **196g** came from the deprotection of the acetate group of mixture of acyloins **196c:197c** (93:7) obtained from the indium reduction of **1c**. The mixture of acyloins **196c:197c** was treated with  $\text{K}_2\text{CO}_3$  in MeOH to furnish the diol **196g** in 90% yield (Scheme 92).

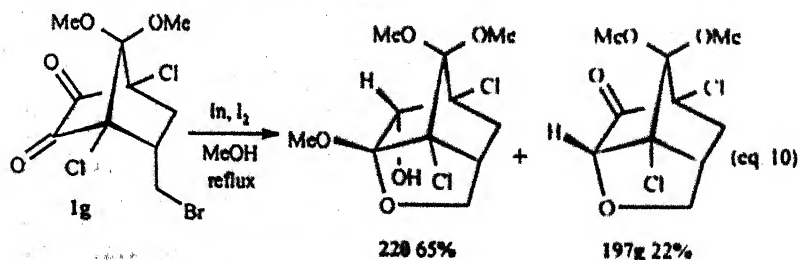
#### Scheme 92



(from **196c:197c**, 93:7 reaction mixture)

The lead tetracetate cleavage of the diol **196g** in 3:1 MeOH-PhH furnished the  $\gamma$ -lactone fused cyclopentanoid derivative **213g** in high yield. The product **197g** and **139** were obtained as a colorless solid and an inseparable mixture in a ratio of 60:40, recorded from the  $^1\text{H}$  NMR spectrum (Scheme 90). However, the two compounds were isolated in pure form via two different independent reactions, the formation of **197g** is discussed below (eq. 10).

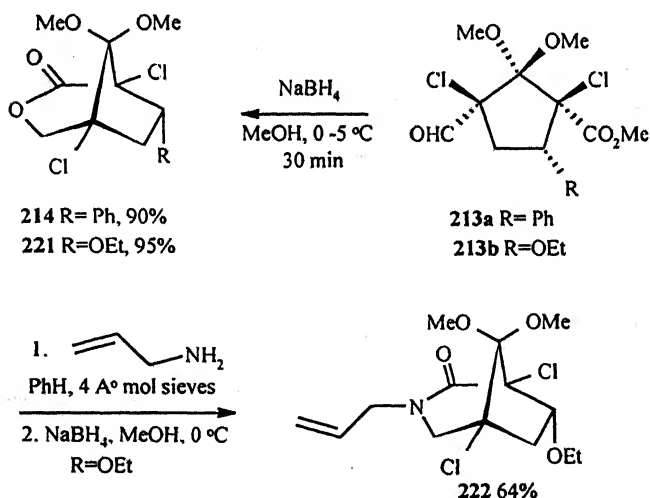
In an attempted indium metal mediated reduction of **1g** in the presence of iodine in anhydrous MeOH under reflux condition, two products **220** and **197g** were acquired in high yield (eq. 10). Both the compounds **197g** and **220** show characteristic W-coupling of 2.0 Hz in  $^1\text{H}$  NMR spectrum. The indium reduction and subsequently the intramolecular displacement was taking place leading to major alcohol **220** and minor oxa tricycle **197g**.



The fact that reaction proceeds via the reduction of the  $\alpha$ -diketone **1g** was further proved by separately treating the  $\alpha$ -keto hemiacetal **120a** with indium in aqueous MeOH under reflux condition for 42 h. The reaction fails with the recovery of the starting material (Scheme 92).

Having achieved the functionalized cyclopentane carboxaldehydes **213** and **215** we performed various reactions, which are presented in Schemes 93 and 94. The bicyclic lactones [3.2.1] **214**, **221** and lactam **222** were conveniently prepared. The sodium borohydride reduction of the aldehydes **213a** and **213b** furnished the bicyclic [3.2.1] lactones **214** and **221** in excellent yields by cyclization of the resulting alcohol (Scheme 93). A one-pot synthesis of bicyclic amide **222** was also easily achieved. The aldehyde **213b** was condensed with allyl amine and the resulting imine was reduced with  $\text{NaBH}_4$  in the same pot to provide bicyclic [3.2.1] lactams **222** in 64% of yield (Scheme 93).

**Scheme 93:** Synthesis of bicyclic [3.2.1] lactones and lactams



Indium promoted allylation<sup>74</sup> was conducted with the aldehydes **213a,b** and **215b** (Scheme 94). While sodium borohydride reduction of

these aldehydes exclusively furnish the lactones **214** and **221**; interestingly, allylindation proceeds with high diastereoselection, but reversal in selectivity was observed by switching ethoxy derivatives **213b**, **215b** to phenyl derivative **213a**. When the ethoxy substituted aldehydes **213b**, **215b** were subjected to Barbier type allylation with indium metal, allyl bromide in DMF at room temperature, the major diastereomer formed from **213b**, **215b** lactonized to give near quantitative yields of a single regioisomer **223b** and **225b** respectively. On the other hand there is significant alteration in selectivity with phenyl substituted derivative **213a**, leading to 82:18 mixture of diastereomers, **224a** as the major product and the lactone **223a** was the minor product. The product distribution in each case was determined from 400 MHz  $^1\text{H}$  NMR of the unpurified reaction prior to column purification. In  $^{13}\text{C}$  NMR, the carbinol carbon for alcohol **224a** appeared at 85.8 ppm, for the lactone **223a**,  $\text{C}_6$  experienced downfield shift, appearing at 89.2 ppm. Three singlets for OMe were seen in  $^1\text{H}$  NMR spectrum for the cyclopentane derivative **224a**. Clear cross peaks between OMe and allylic  $\text{CH}_2$  in 500 MHz  $^1\text{H}/^1\text{H}$  NOESY spectrum confirms the relative stereochemistry in lactones **223a** and **223b**. The NOE correlations from  $^1\text{H}/^1\text{H}$  NOESY spectrum of **223a,b** are shown in Figure 9. The  $^1\text{H}/^1\text{H}$  NOESY spectrum of **223a,b** is presented in Figure 10, 11. The connectivity is indicated on the spectrum. The connectivity was further established unambiguously using HMBC, HMQC, and HETCOR.

## Scheme 94: Allyl indium addition to cyclopentane carboxaldehydes

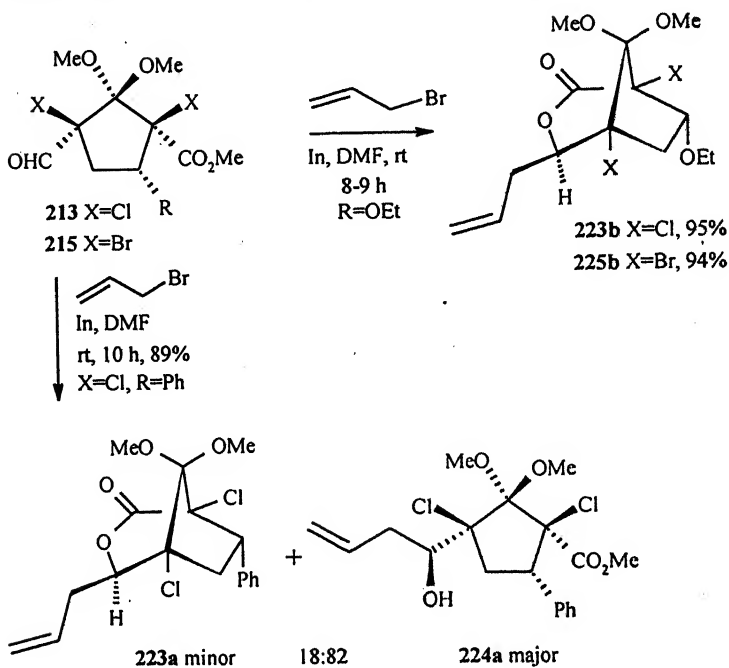
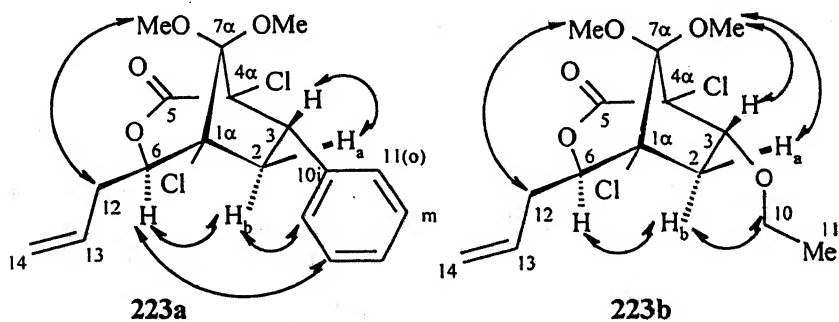
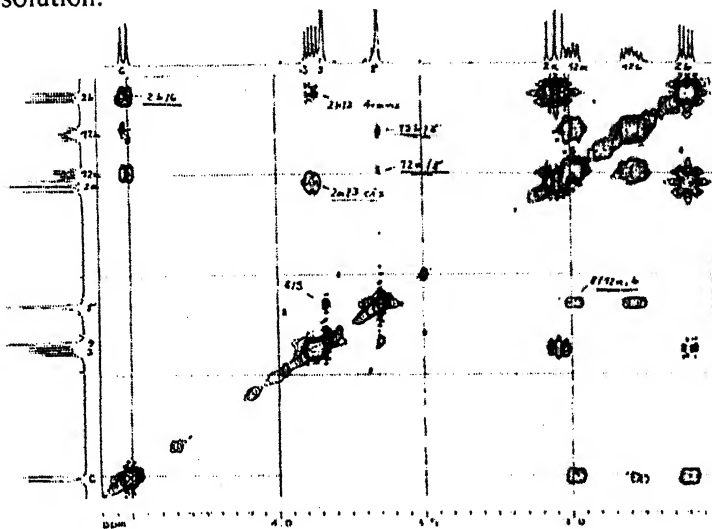


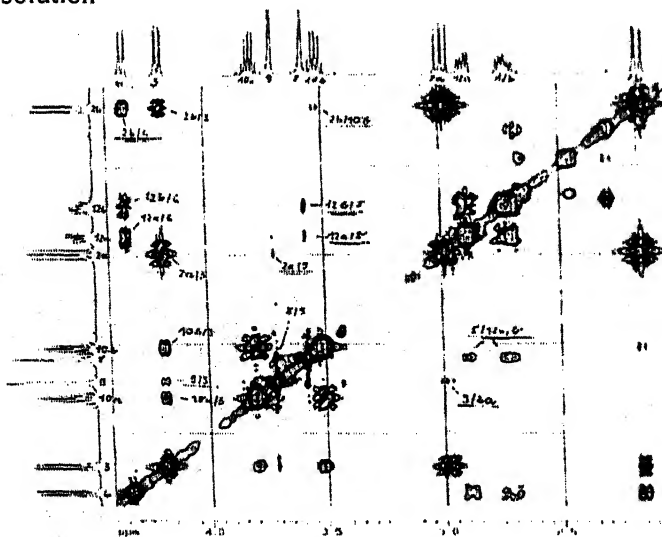
Figure 9: NOESY correlations of 223a,b



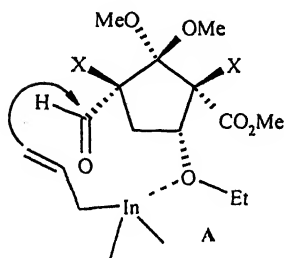
**Figure 10:** 500 MHz  $^1\text{H}/^1\text{H}$  NOESY spectrum of 223a in  $\text{CDCl}_3$  solution.



**Figure 11:** 500 MHz  $^1\text{H}/^1\text{H}$  NOESY spectrum of 223b in  $\text{CDCl}_3$  solution



The stereochemical outcome of allylindium addition to  $\alpha$  and  $\beta$ -oxy substituted aldehydes were extensively investigated by Paquette.<sup>85</sup> The aldehydes **213** and **215** possess a  $\gamma$ -alkoxy substituent and is capable of chelating with the allylindium reagent for the observed selectivity leading to *syn* alcohol which lactonizes, as shown in A.



## Conclusion

In summary, we have described a novel, efficient and regio- as well as diastereoselective conversion of non-enolizable bicyclic  $\alpha$ -diketones into synthetically useful acyloins mediated by indium metal, tolerable to a variety of sensitive substituents such as acetate, ester and bridgehead halogens. Further the methodology is extended to the synthesis of highly functionalized cyclopentane carboxaldehydes, potential building blocks in organic syntheses via cleavage of the acyloins under  $\text{Pb}(\text{OAc})_4/\text{MeOH-PhH}$  conditions. The allylindium addition to carboxaldehydes were found highly diastereoselective, the selectivity was altered from ethoxy derivative to phenyl derivative.



## Chapter 3B

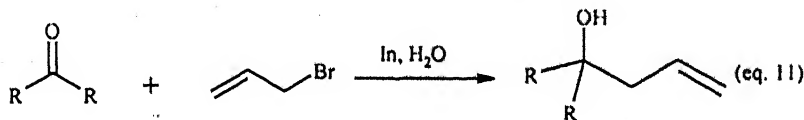
### Diastereoselection during allylindium addition to norbornyl $\alpha$ -diketones

#### 1. Introduction

Indium mediated Barbier-type reaction to form carbon-carbon bond has emerged as one of the exciting areas in organic synthesis.<sup>74</sup> Since its discovery by Butsugan,<sup>86</sup> the allylindium addition to carbonyl compounds has found wide-ranging current interest, and generally proceeds with high levels of chemo-, regio- and stereoselectivity.<sup>74</sup> These coupling reactions were performed at ambient temperature in organic or even aqueous solvents, which obviates the need of "dry reaction condition" to furnish the homoallylic alcohols in high yield operated by a single electron transfer mechanism. The sensitivity of the organometallic reagents such as Grignard,<sup>87</sup> organolithium,<sup>88a</sup> alkyltitanium,<sup>88b</sup> and allylchromium reagents,<sup>88c</sup> to moisture requires their addition reactions to be performed in anhydrous organic solvents. Therefore in comparison with other metals, the unique properties associated with indium metal, particularly, the insensitivity towards air or moisture, proved it to be a significant, and advantageous approach for C-C bond forming reactions. The allylindium reagents are compatible with protic solvents and can be easily generated in water and combinations of water and miscible organic solvents. The other attractive features include the mild nature of the allylindium reagent, which shows no dimeric hydrocarbons as by products from bromides;

and show chelation controlled high stereoselectivities even in aqueous medium. Diastereoselectivity in allylation reactions has been a topic of continuous discussion.<sup>89</sup>

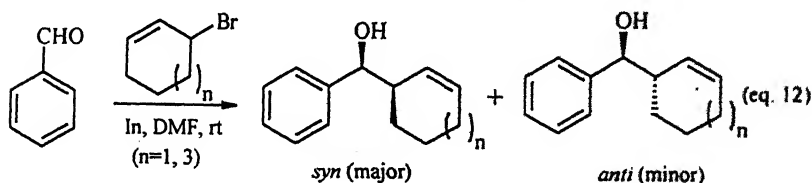
Butsugan and coworkers first demonstrated the allyl and substituted allyl reagents (crotyl, methallyl, cinnamyl, etc.), add to aldehydes to give the homoallylic alcohols in high yield.<sup>86</sup> Li and Chan subsequently reported the feasibility of allylindium addition in water with aldehydes and ketones (eq. 11).<sup>74c,90</sup> Indium mediated allylations with substituted allyl bromides are highly  $\gamma$ -selective.<sup>91</sup> A single electron transfer mechanism was suggested for these coupling reactions. The diastereoselection of these additions was dependent on the substituents on the allyl indium reagent as well on the substrate and was extensively studied by Paquette and coworkers.<sup>85,92</sup>



We for the first time studied highly diastereoselective addition of cyclohex-2-enyl and cyclooct-2-enyl indium to a variety of aromatic aldehydes.<sup>83</sup> The indium-mediated allylation addition of 3-bromocyclohexene and 3-bromocyclooctenes to a variety of aromatic aldehydes and cyclohexanone proceeds smoothly with excellent *syn* diastereoselectivity to produce the corresponding cycloalkenyl substituted homoallylic alcohols in good to high yield (eq. 12).

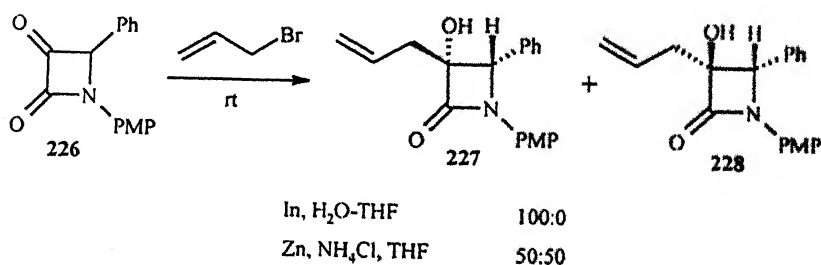
However, although recently Indium has been extensively used in carbonyl addition reactions, the chemistry of 1,2-diketones towards

this reagent remains unexplored. When we started our study on allylindium addition to  $\alpha$ -diketones, there were no reports on indium-mediated allylation to 1,2-diones, however there are three reports which appeared very recently and are summarized below.



Bose and coworkers applied the allylation of azetidin-2,3-dione **226** with indium in the synthesis of  $\alpha$ -allyl  $\beta$ -lactams **227** (Scheme 95).<sup>93</sup> The reaction proceeds with high yield leading to exclusive formation of a single diastereomer (*anti*, **227**), in which Zn often provides a 1:1 mixture of diastereomers, **227** and **228**. Paquette's group also extensively studied the related reaction.<sup>94</sup>

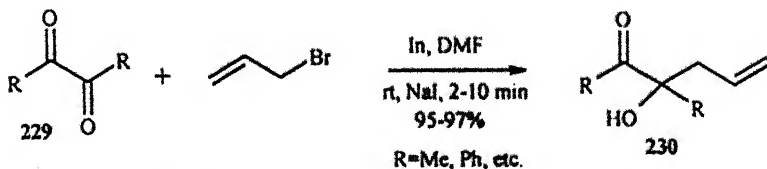
Scheme 95: Allylation reaction with azetidin-2,3-diones



Indium mediated allylation and cinnamylation of 1,2-diketones **229** in the presence of NaI was reported by Nair *et al.* leading to the  $\alpha$ -carbonyl homoallylic alcohols **230** in high yield (Scheme 96).<sup>95</sup> The

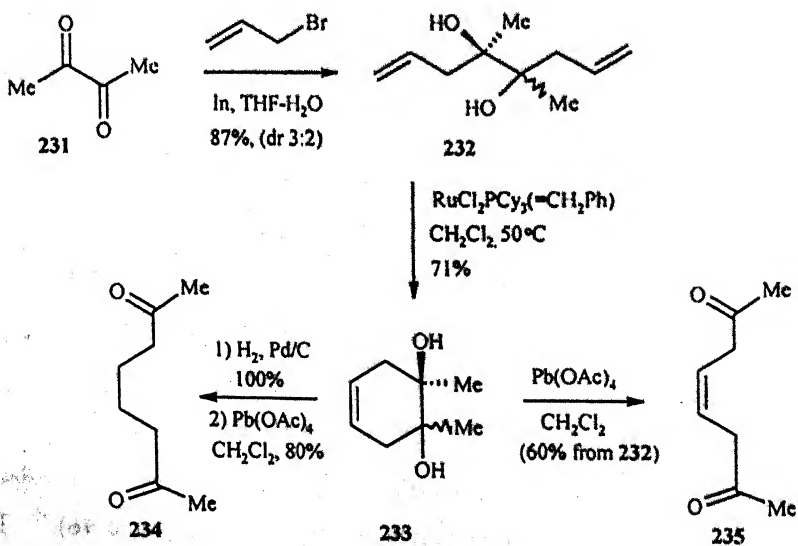
cinnamylindium addition often furnished a mixture of  $\alpha$  and  $\gamma$ -regioisomers depending on substituents.

Scheme 96

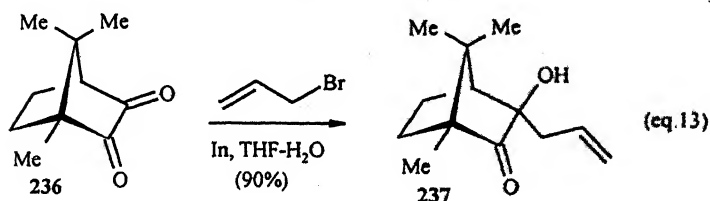


While exclusively mono allylation products were obtained by giving less reaction time (few minutes) and using 1.05 mmol of Indium powder in DMF (Scheme 96), more recently Paquette reported allylindation at both the adjacent carbonyls by using excess powdered Indium metal in aqueous THF (Scheme 97).

Scheme 97

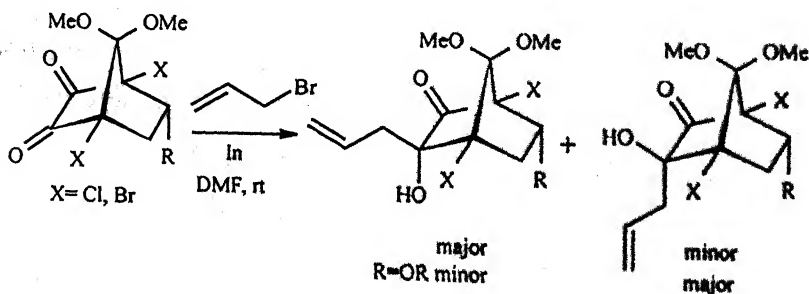


The diallylated products **232** of biacetyl **231** was further used for the synthesis of saturated and unsaturated 1,6-diketones **234** and **235** via ring closing metathesis and cleavage of the resulting diol **233** (Scheme 97). However, the allylindiation of camphorquinone **236** was taking place from the *endo* face leading to the exclusive formation of the monoallylation product, the *exo* alcohol **237** (eq. 13).



Although there are two recent reports by Nair and Paquette, which appeared after we started our study, our objective was to study the allylindium addition to dihalonorbornyl 1,2-diketones in the presence of chelating and non-chelating *endo* substituents. We observed high level of regio- and diastereoselection, and a heteroatom, e.g., oxygen atom directly attached to norbornene skeleton induces reversal in selectivities (Scheme 98).

**Scheme 98:** Allylindium addition to dihalonorbornyl  $\alpha$ -diketones



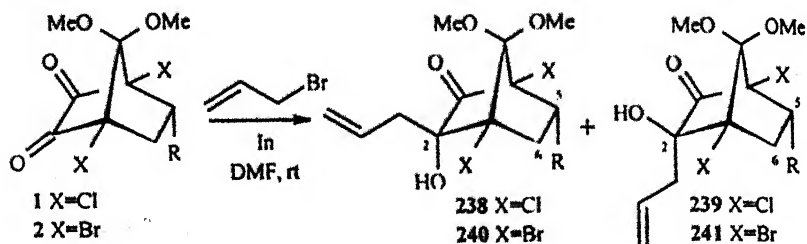
## 2. Results and Discussion

The encouraging results of indium mediated efficient reduction of norbornyl  $\alpha$ -diketones (Chapter-3A), with high regio and diastereoselectivity, driven us to study the allylindium addition to the diketones in the presence of chelating and non-chelating *endo* substituents. The reaction procedure was simple. The diketones were subjected to 2 equivalent of Indium metal and allylbromide in DMF at room temperature to furnish the corresponding  $\alpha$ -keto homoallylic alcohols in excellent yields, arising from allylation of one of the carbonyl groups (Table 5 and 7).

**2.1 Monosubstituted  $\alpha$ -diketones:** The reaction was particularly found to be interesting for monosubstituted diketones **1a-f**, **2a,b,d,f** leading to the corresponding two diastereomeric allylation products **238,239** for chloro derivatives; and **240,241** for bromo derivatives. The results are summarized in Table 5. The yields and diastereoselectivities were found to be consistently high. The reactions were highly regioselective. In all cases, the allyl group is transferred to the less congested carbonyl group diagonal to the *endo* substituent. The diastereoselectivities of the reactions were found to be greatly dependent on *endo* substituents (Table 5). While allylindium addition is taking place exclusively from *endo* face in case of camphorquinone (eq.13), interestingly the *exo* addition is favored in case of **1a**, **2a**, **1c** and **1e** leading to the corresponding *endo* alcohols **238,240** as the major product (entries

1,2,5,8 Table 5). The *exo* alcohols 239,241 were formed as the minor products.

In contrast to 1a, 2a, 1c and 1e, a significant reversal of product stereoselectivity was observed when allylindium addition was performed with *endo* ethoxy 1b,2b and *endo* acetoxy 1d,2d derivatives. The product distribution in 1b,2b and 1d,2d was now in favor of *exo* isomer, the crossover suggesting that chelate control may be operating (entries 3,4 and 6,7; Table 5). Further, the heteroatom directly attached to the norbornyl derivative induces the opposite selectivity as evidenced from the results obtained by switching from *endo* CH<sub>2</sub>OAc substituent (entry 5, Table 5) to *endo* OAc derivative (entry 6,7; Table 5). The diketone having *endo* CH<sub>2</sub>OAc substituent 1c furnished 77:23 ratio of *endo:exo* alcohols (238a:239a); while the chloro *endo* OAc derivative 1d gave an exact reversal in selectivity, i.e., 23:77 mixture of carbinols 238a,239a. Similar reversal in selectivity in favor of *exo* alcohol was observed for 1b,2b and 2d. The diastereomeric ratios varied from 91:9 to 14:86 of *endo:exo* alcohols. The allylations involving *endo* methyl ester derivatives 1,2f was not selective giving diastereomeric ratios of corresponding acyloins 238f,239f and 240f,241f nearly equal to 50:50. The diastereomeric ratios, in all cases were determined by <sup>1</sup>H NMR integration at 400 MHz of 238,239 and 240,241 mixtures prior to their chromatographic separation.

**Table 5.** Indium mediated allylation of monosubstituted  $\alpha$ -Diketones to acyloins<sup>a</sup>

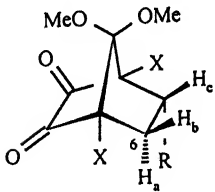
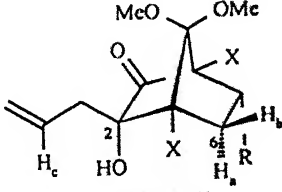
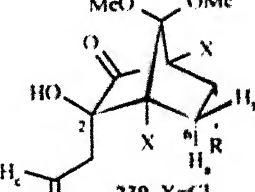
Entry	Substrate	R	Time (h)	Yield (%) <sup>b</sup>	Product Ratio* (endo:exo) <sup>c</sup>
1	1a, X=Cl	Ph	4	94	82:18
2	2a, X=Br	Ph	6	93	89:11
3	1b, X=Cl	OEt	3.5	93	14:86
4	2b, X=Br	OEt	5	94	18:82
5	1c, X=Cl	CH <sub>2</sub> OAc	1.5	71	77:23
6	1d, X=Cl	OAc	5	92	23:77
7	2d, X=Br	OAc	5	91	25:75
8	1e, X=Cl	SiMe <sub>3</sub>	5	91	91:9
9	1f, X=Cl	CO <sub>2</sub> Me	6	92	43:57
10	2f, X=Br	CO <sub>2</sub> Me	5	94	45:55

<sup>a</sup> All reactions were performed using 2 eq. indium metal by vigorously stirring with allylbromide in DMF; <sup>b</sup> Isolated yields of analytically pure alcohols; <sup>c</sup> The product distributions in all cases were determined by <sup>1</sup>H NMR integration at 400 MHz of the unpurified product mixtures.

\*For X=Cl, 238:239, For X=Br, 240:241



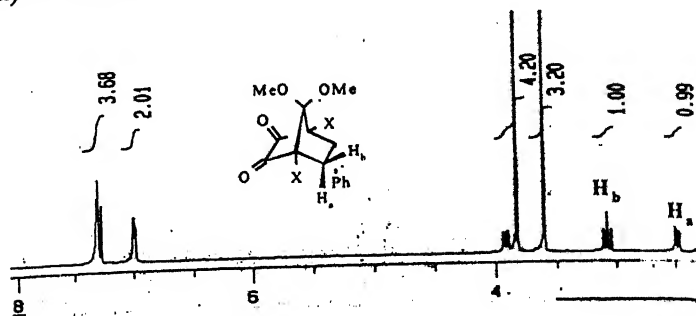
**Table 6:** Comparison of  $^1\text{H}$  NMR chemical shift values of  $\text{H}_a$ ,  $\text{H}_b$  in monosubstituted diketones and the corresponding acyloins. ( $\delta$ -values in ppm at 400 MHz ( $\text{CDCl}_3$  solution))

 <p>1 X=Cl 2 X=Br</p>	 <p>238 X=Cl 240 X=Br</p>	 <p>239 X=Cl 241 X=Br</p>			
Diketone	H <sub>a</sub>	H <sub>b</sub>	Acyloin	H <sub>a</sub>	H <sub>b</sub>
1a	2.48	3.07	238a	3.13	2.76
			239a	2.46	3.20
2a	2.53	3.13	240a	3.22	2.89
			241a	2.46	3.30
1b	2.13	2.98	238b	2.64	2.77
			239b	2.26	2.98
2b	2.18	2.99	240b	2.78	2.98-2.79
			241b	2.38	2.90
1c	2.18	2.75	238c	2.60	2.51
			239c	2.25	2.67
1d	2.06	3.14	238d	2.74	2.84
			239d	2.20	2.98
2d	2.12	3.18	240d	2.65	2.83
			241d	2.30	3.09
1e	1.90	2.19	238e	1.91	2.35
			239e	2.06-2.00	

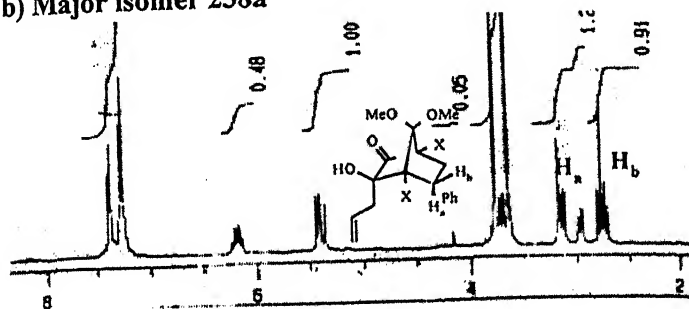
An unequivocal confirmation to the stereochemistry of the *endo* alcohols **238** and **240**, was available from the  $^1\text{H}$  NMR spectral analysis. The effect of *endo*-OH at  $\text{C}_2$  on the *endo*- $\text{H}_6$  was quite revealing (Table 6). Our own findings on indium-mediated reduction of  $\alpha$ -diketone demonstrated that the presence of an *endo*-oxygen substituent at  $\text{C}_2$  has a remarkable deshielding effect on the *endo*- $\text{H}_6$ . The *exo*- $\text{H}_6$  also experiences a shielding effect. The comparison of  $^1\text{H}$  NMR (400 MHz) values of *exo* and *endo*- $\text{H}_6$  of acyloins **238-240** with those of the parent  $\alpha$ -diketones **1,2** confirms the stereochemical assignments. In compounds **238** and **240**, the *endo*- $\text{H}_6$  clearly showed significant deshielding effect ranging from 0.5 to 0.7 ppm while the *exo*- $\text{H}_6$  is shielded consistently by 0.21 to 0.31 ppm. The deshielding effect of *endo*- $\text{H}_6$  was more pronounced in  $\alpha$ -keto homoallylic alcohols **238,240** than the corresponding acyloins **196,198** (Chapter 3A) resulting from the indium-mediated reduction (the range was 0.2 to 0.5 ppm). This effect was found more pronounced in case of chloro derivatives (entry 1 and 5). Figure 12a-c presents the 400 MHz  $^1\text{H}$  NMR spectra of **1a**, **238a**, and **239a**. A minimal deviation was observed for their counterparts in the *exo* series **239,241** (Table 6), i.e.; the deshielding of  $\text{H}_a$  and shielding of  $\text{H}_b$  from 0.07-0.2 ppm. The distinction applies to allylic  $\text{CH}_2$  protons as well, each of which are clearly visible as doublet of  $\frac{1}{2}\text{ABq}$  (in most cases) in the downfield ( $\delta$  2.99-2.67 ppm) for *endo* alcohols **238,240**, than their *exo* counterparts **239,240** ( $\delta$  2.39-2.74 ppm).

**Figure 12:** Comparison of  $^1\text{H}$  spectrum (400 MHz) showing the deviation of  $H_a$ ,  $H_b$  values of major 238a and minor 239a isomer with that of parent diketone 1a.

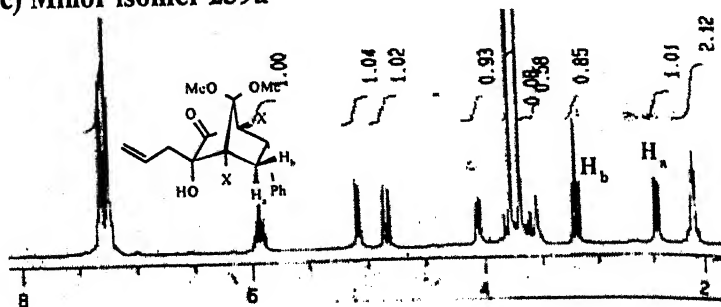
a)  $\alpha$ -diketone 1a



b) Major isomer 238a

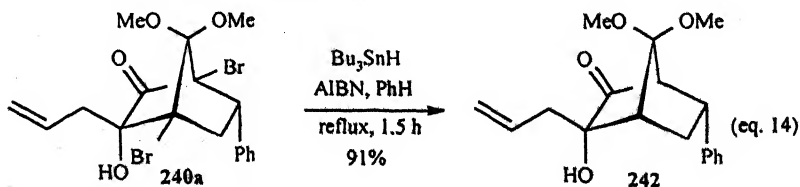


c) Minor isomer 239a



In case of phenyl derivatives **239a** and **241a**, the allylic protons shielded more strongly, appearing as a multiplet at  $\delta$  2.06–2.20 ppm. The spin decoupling experiment was carried out to unambiguously assign the allylic protons,  $H_a$  and  $H_b$  (see experimental section). The irradiation of  $H_c$  resulted the disappearance of its coupling with allylic  $CH_2$  protons. The vinylic proton  $H_c$  of **238,240**, also experienced a little deshielding effect ( $\sim$ 0.10–0.19 ppm) than **239,241**. In  $^{13}C$  NMR, the allylic carbon for *endo* alcohols **238,240** appeared at 39.6–42.1 ppm, while for their *exo* counterparts **239,241**; the allylic carbon showed upfield at 36.2–37.0 ppm.

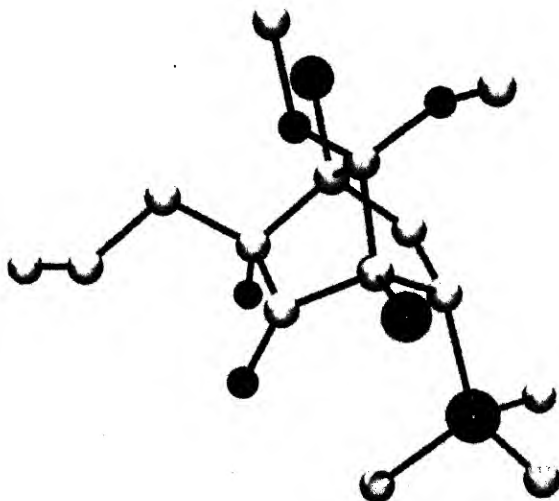
Further structural proof for the formation of *endo* isomers came from the 2D NMR spectrum (COSY, NOESY, HMBC, HMQC) of the carbinol **242** obtained from the bridgehead reduction of *endo* phenyl derivative **240a** (eq. 14). The bridgehead reduction of **240a** using TBTH in benzene was purposely carried out to see further couplings of bridgehead hydrogen. The  $^1H$  NMR spectrum shows a diagnostic W-coupling of 1.9 Hz between  $H_4$  and  $H_b$ . The  $^1H/^1H$  NOESY spectrum of **242** is presented in Figure 13. The NOE correlations from  $^1H/^1H$  NOESY spectrum of **242** were shown in Figure 14, which confirmed the structure of *endo* alcohol.



NOE's: 2a/3 (*cis*), 4/3 (*cis*), 2a/1 (*cis*), 2b/OH, 2b/11(o), 9/3, 9/2a, 9/4, 8/14a,b, 8/15a,b, 8/4.

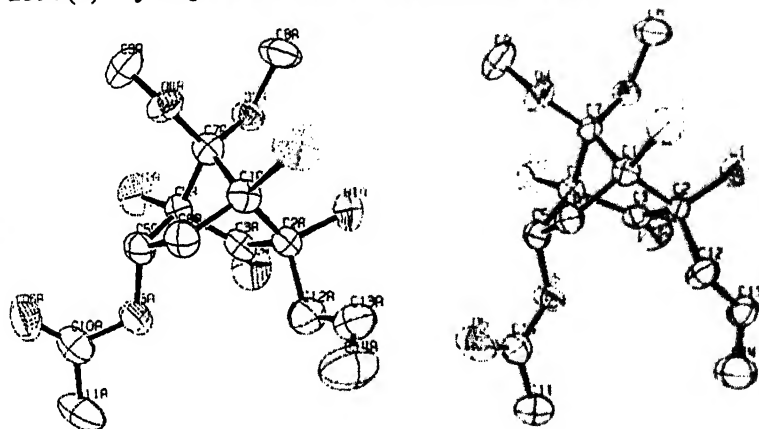
**X-ray structural studies:** The shielding effect of vicinal  $\text{SiMe}_3$  group overrides the deshielding effect of *endo* OH group on protons attached to C(6) carbon (Table 6). The unequivocal identification of the major product (the *endo* alcohol) was made on the basis of X-ray crystallographic analysis of **238e** (Figure 15).

**Figure 15:** POV-ray diagram of **238e**. Hydrogen atoms are excluded for clarity; (gold=carbon, red=oxygen, deep pink=silicon, green=chlorine).



The unequivocal proof for the major *exo* alcohol **239d** was further confirmed with the help of X-ray crystal structure of compound, while minor **238d** was confirmed *endo* on the basis of chemical shift values of allylic protons, *exo*-H<sub>6</sub> and *endo*-H<sub>6</sub> protons (Table 6). Figure 16 represents the ortep diagram of **238d**. The structure of **238d** reveals two crystallographically independent molecules in the unit cell.

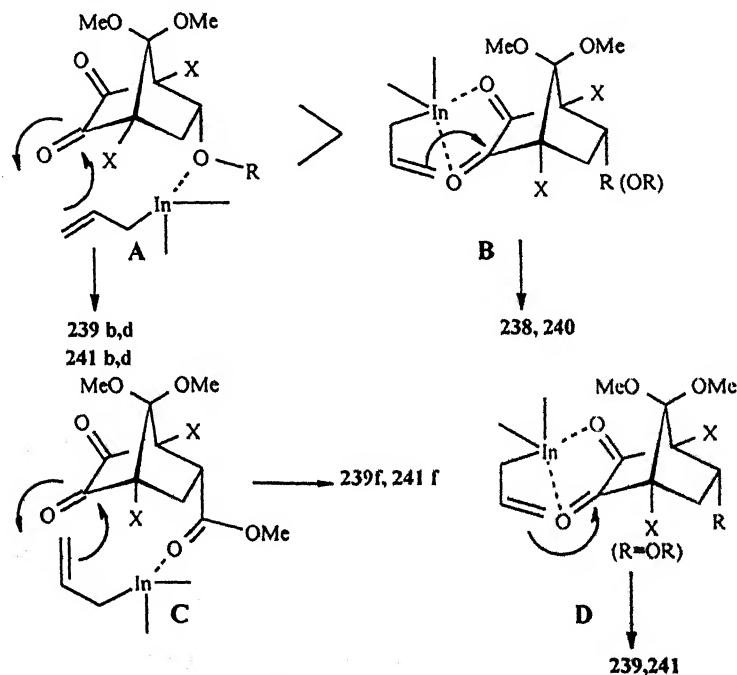
**Figure 16:** Crystal structure of compound **239d**, showing two crystallographically independent molecules: left, **239d** (1), right **239d**(2). Hydrogen atoms are excluded for clarity.



**Mechanistic considerations:** The diastereofacial selectivity of the allylindium addition depends on the *endo* substituents on the  $\alpha$ -diketones. The formation of *endo* alcohols **238** and **240** could be explained as shown in B (Figure 17), the coordination of the allylindium reagent to both carbonyl oxygen of the diketone followed by *exo* addition to sterically less congested carbonyl group furnishes the products. We believe that the reversal of selectivity in acetoxy and ethoxy derivatives **1b**, **2b** and **1d**, **2d** leading to the predominant products as *exo* alcohols **239 b,d** and **241 b,d** is possibly because of the chelation of the indium reagent to the heteroatom directly attached to the norbornyl derivatives (shown in A, Figure 17). Reversal in

selectivity in going to  $\text{CH}_2\text{OAc}$  derivative **1c** further supports our assumption. The formation of 1:1 mixture of alcohols **1f**, **2f** from the *endo* methyl ester derivatives could presumably be due to the chelation of the indium reagent to the ester carbonyl (shown in C).

**Figure 17**

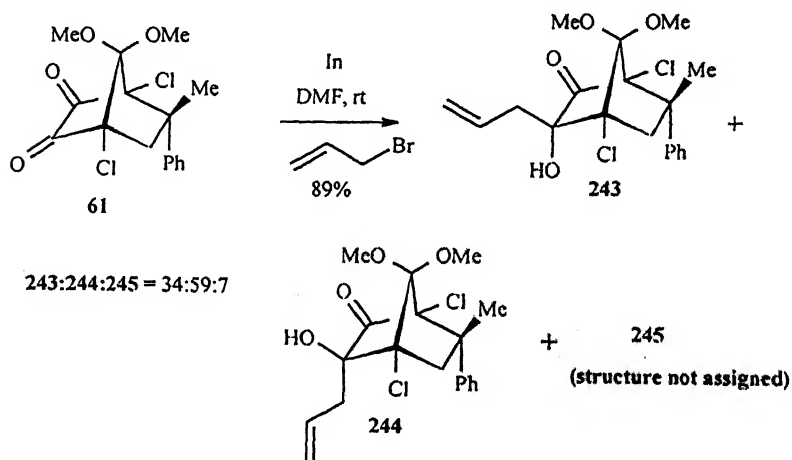


When an electron-donating Me group was placed at C(5) in **1a**, a significant alteration in diastereoselection was observed during allyl indium addition of **61** in comparison to **1a**. Three products were observed in a ratio of 34:59:7 from  $^1\text{H}$  NMR spectrum of the crude reaction mixture prior to column purification (Scheme 99). We could not assign the structure for the major two compounds **243** and **244**,



with the diastereoselection in favor of the *exo* alcohol **244**. The presence of an *exo* substituent, apparently, has an effect on the outcome of addition; there was a reversal in the selectivity compared to that of **1,2a**. The addition from *exo* face was diminished and possibly the major alcohol **244** was derived from addition to *endo* face as shown in D. The products **243** and **244** were characterized on the basis of their  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectrum.

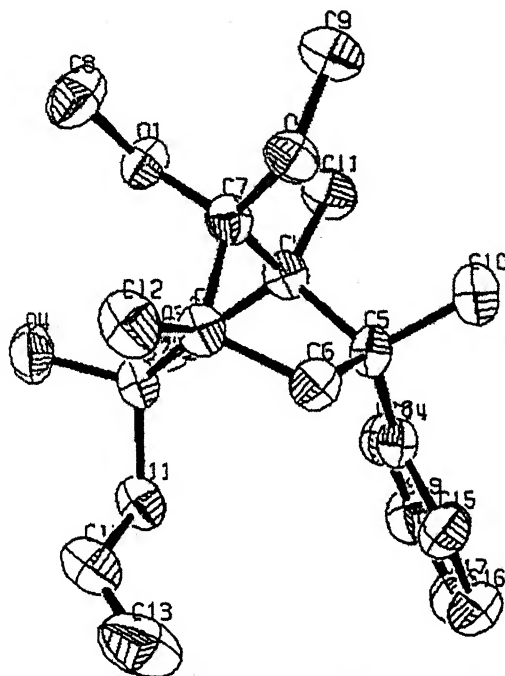
**Scheme 99:** Allylindium addition to the diketone **61**



In  $^1\text{H}$  NMR spectrum the allylic  $\text{CH}_2$  protons are clearly visible as two doublets of  $\frac{1}{2}\text{ABq}$  in the downfield region ( $\delta$  2.77-2.60 ppm) for *endo* alcohols **243**, while for *exo* alcohol **244** they are strongly shielded ( $\delta$  1.89-1.71 ppm) due to the presence of phenyl group. Similarly, the characteristic upfield shift of allylic  $\text{CH}_2$  carbon for major *exo* alcohol **244** which appears at 36.8 ppm while the same for *endo* alcohol shows at 39.9 ppm. Further, for *exo* alcohol **244**,  $\text{C}_7$  was relatively deshielded,

similar to the *exo* alcohols 239,241 and appears at 105.6 ppm. Further the structure of major *exo* alcohol 244 was confirmed by X-ray crystal structure. The ortep diagram is shown in Figure 18.

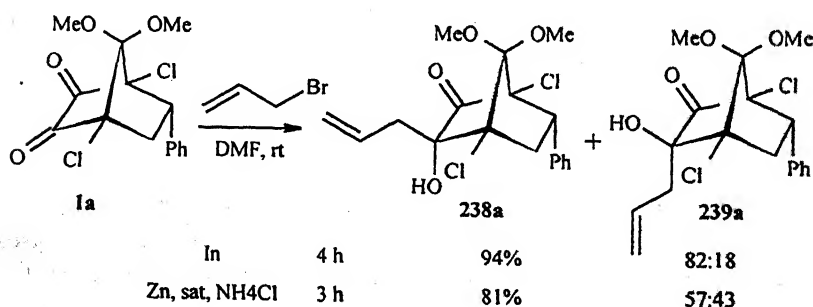
**Figure 18:** Ortep diagram of 244. Hydrogen atoms are excluded for clarity.



**Allylation under different conditions:** The diastereomeric ratios resulting from exposure of diketones to allyl bromide and indium in different solvents are compiled in Table 7. For substrates studied, constant diastereoselectivities were realized whether water is present or not (entries 4-5,8-121). Thus, the *endo* ethoxy and acetoxy substituents are capable of exerting chelation control, irrespective of whether the

allylation is performed in an anhydrous or aqueous medium. By carrying out the reaction under acidic medium (entries 2, 7), the phenyl derivative **1a** shows as such no response, giving rise to almost same product distribution (entry 1,2) while the diastereoselection in case of ethoxy derivative **2b** was increased up to 7% in favor of *endo* alcohol. The use of additive such as addition of 1 mol equiv of LiF to phenyl derivative **1a** has least effect (entry 3), and is similar to the reaction with 2:1 DMF:10% HCl (entry 2). Using excess reagent (entry 6), only the monoallylation product was detected, without any change in diastereoselectivity or yield of the reaction. The reaction was completed within 1h for **2b** (entry 6). The outcome was also found to be same, giving longer reaction time of 20 h with excess reagent. The coupling of diketones with allylbromide in the presence of indium provides high yield and diastereoselectivity irrespective of solvent employed.

**Scheme 100: Allylation of diketone 1a**



For comparison purpose, Zn mediated allylation was performed on **1a**. Treatment of **1a** with allylzinc in 1:1 sat. NH<sub>4</sub>Cl and DMF at room temperature afforded **238a** and **239a** in a ratio of 57:43 in 83% of

yield (Scheme 100). The use of Zn worsens the diastereoselectivity, while high diastereoselection, 82:18 of **238a** and **239a** was achieved by indium mediated allylation reaction.

**Table 7:** Indium promoted allylation in different solvents.

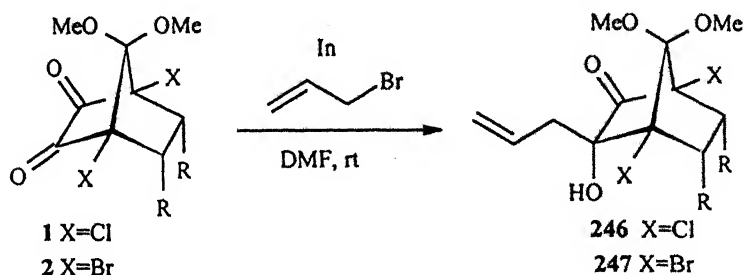
Entry	Substrate R	Solvent	Time (h)	Yield (%) <sup>b</sup>	Product Ratio <sup>a,c</sup>
1	<b>1a</b> , Ph	DMF	4	94	82:18
2	<b>1a</b> , Ph	DMF:10%HCl(2:1)	3	91	84:16
3	<b>1a</b> , Ph	DMF	5	92	84:16 <sup>d</sup>
4	<b>1b</b> , OEt	DMF	3.5	93	14:86
5	<b>1b</b> , OEt	THF:H <sub>2</sub> O (1:1)	9	94	14:86
6	<b>2b</b> , OEt	DMF	1	93	18:82 <sup>e</sup>
7	<b>2b</b> , OEt	DMF:10%HCl(2:1)	8	91	25:75
8	<b>2b</b> , OEt	DMF:H <sub>2</sub> O (1:1)	3.5	93	17:83
9	<b>1d</b> , OAc	DMF	5	93	25:75
10	<b>1d</b> , OAc	DMF:H <sub>2</sub> O (1:1)	5	93	25:75
11	<b>2d</b> , OAc	DMF	5	91	25:75
12	<b>2d</b> , OAc	DMF:H <sub>2</sub> O (1:1)	5	91	25:75

<sup>a</sup> All reactions were performed using 2 eq. indium metal by vigorously stirring with allylbromide in DMF; <sup>b</sup> Isolated yields of analytically pure alcohols; <sup>c</sup> The product distributions in all cases were determined by <sup>1</sup>H NMR integration at 400 MHz of the unpurified product mixtures; <sup>d</sup> DMF, LiF; <sup>e</sup> using excess In metal (3 eq.) and 5 eq. allylbromide.

\*For 1 X=Cl, 238:239, For 2 X=Br, 240:241

**2.2 Allylindium addition to disubstituted  $\alpha$ -diketones:** The allylindium addition to disubstituted  $\alpha$ -diketones proceeds with a high level of diastereoselection. A single diastereomer was obtained for disubstituted derivatives **1i-l,t,v** and **2i-k,t,v**. The *endo* alcohols **246 i-l,t,v** and **247i-k,t,v** were exclusively formed with excellent yield (Table 8). From the  $^1\text{H}$  NMR spectrum (400 MHz), a sharp singlet was observed for hydroxyl group ( $\text{D}_2\text{O}$  exchangeable), for all *endo* alcohols derived from mono and disubstituted derivatives. This is consistent with our observation for the monosubstituted alcohol **238a**, where the hydroxyl singlet was found at 3.17 ppm ( $\text{D}_2\text{O}$  exchangeable). The allylic  $\text{CH}_2$  protons of *endo* alcohols **246,247**, are clearly visible as dd (in most cases) in the same downfield range (2.99-2.63 ppm) as for *endo* alcohols **238,240**. In  $^{13}\text{C}$  NMR, the allylic carbon appears at 40.4-43.7 ppm.

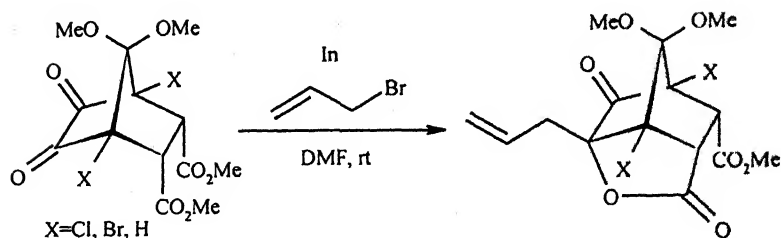
The diester derivatives **1,2m** and **205** underwent subsequent cyclization after the initial allylindium addition leading to the corresponding lactones **248-250** (Scheme 101). These results further confirmed the exclusive formation of *endo* alcohols from the allylindium addition to the disubstituted  $\alpha$ -diketones. The  $^1\text{H}$  NMR spectrum shows three singlets for OMe and  $^{13}\text{C}$  NMR shows the carbonyl groups at 190.5-200.7 ppm, the lactone carbonyls at 170.6 to 173.9 ppm and the ester carbonyls at 166.9-169.6 ppm for **248-250**.

**Table 8.** Indium mediated allylation of disubstituted  $\alpha$ -Diketones to acyloins<sup>a</sup>

Entry	Substrate	R	Product	Time (h)	Yield <sup>b</sup> (%)
1	1i, X=Cl	-(CH <sub>2</sub> ) <sub>3</sub> -	246i	6	97
2	2i, X=Br	-(CH <sub>2</sub> ) <sub>3</sub> -	247i	7	98
3	1j, X=Cl	-(CH <sub>2</sub> ) <sub>4</sub> -	246j	8	96
4	2j, X=Br	-(CH <sub>2</sub> ) <sub>4</sub> -	247j	7	97
5	1k, X=Cl	-(CH <sub>2</sub> ) <sub>5</sub> -	246k	5	96
6	2k, X=Br	-(CH <sub>2</sub> ) <sub>5</sub> -	247k	5	97
7	1l, X=Cl	-(CH <sub>2</sub> ) <sub>6</sub> -	246l	6	98
8	1t, X=Cl	-CH <sub>2</sub> OCH <sub>2</sub> -	246t	5	95
9	2t, X=Br	-CH <sub>2</sub> OCH <sub>2</sub> -	247t	6	95
10	1v, X=Cl	CH <sub>2</sub> OAc	246v	10	98
11	2v, X=Br	CH <sub>2</sub> OAc	247v	9	99

<sup>a</sup> All reactions were performed using 2 eq. indium metal by vigorously stirring with allylbromide in DMF; <sup>b</sup> Isolated yields of analytically pure alcohols

Scheme 101: Allylindium addition of diester derivatives



1m X=Cl	9 h	248 97%
2m X=Br	11 h	249 95%
205 X=H	7 h	250 95%

### 3. Conclusion

Unlike the indium mediated reductions of norbornyl  $\alpha$ -diketones (Chapter 3A), where the reduction was taking place such as to furnish both the possible regioisomers but with exclusive *endo*-acyloins (*endo*-hydroxyl groups), the coupling of the allylindium reagent was highly regioselective; the reagent added solely to the carbonyl group, diagonal to the *endo* substituent. The present study demonstrates the highly diastereoselective addition of allylindium to norbornyl  $\alpha$ -diketones. In case of monosubstituted derivatives also, the reaction was found to be highly diastereoselective; reversal in the diastereoselection was observed on switching to oxygenated *endo*-substituents, connected to norbornyl framework through oxygen atom.

## Conclusion

The synthetically versatile title compounds **norbornyl  $\alpha$ -diketones** were efficiently prepared from easily accessible, celebrated rigid template tetrahalonorbornyl derivatives by a novel, facile and extremely efficient methodology employing catalytic  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$  and  $\text{NaIO}_4$  as stoichiometric cooxidant. The **Chapter I** summarizes the transformation of skeletal carbons of norbornyl core to: (i) five membered carbocycles such as pentenomycin analogues, (ii) azaspiro[4.5]decanone and (iii)  $\gamma$ - and  $\delta$ - lactones (Chart 17). The synthetic strategy involves tailoring of tetrahalonorbornyl skeleton by installing requisite functional groups and structural entities from the Diels-Alder adduct stage making use of the persuasive advantages of stereocontrol in dissection of skeletal bonds. The overall conclusions from Chapter are summarized below:

1) The  $\alpha$ -diketones were elaborated to obtain highly functionalized novel cyclopentane possessing bis( $\alpha$ -chloroester) groups or potential bicyclic lactones, which are inaccessible via the existing methods.

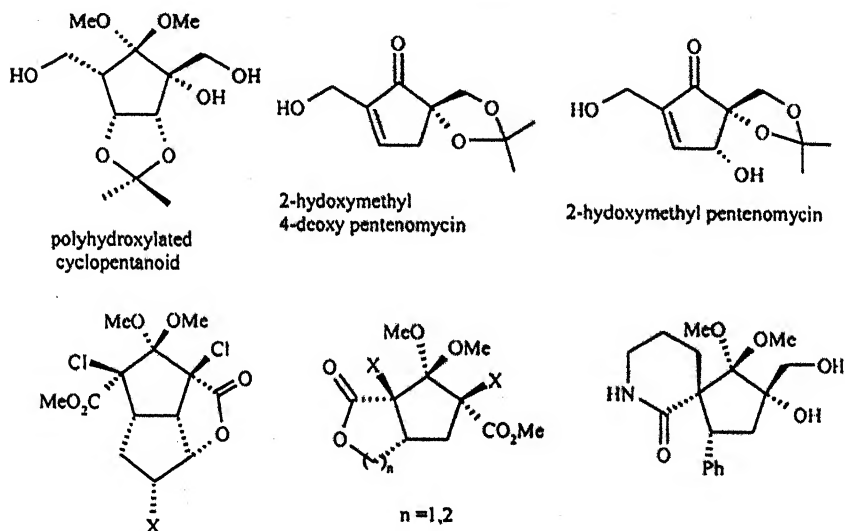
2) The regio- and stereoselective formation of bridged lactones were successfully utilized in the synthesis of polyhydroxy cyclopentane derivatives. We have accomplished a new synthesis of 2-hydroxymethyl 4-deoxy pentenomycin derivative **48**, and a functionalized pentenomycin derivative **49** (**89**) in five and seven steps



in an overall yield of 41.3% and 20.6%, respectively, starting from tetrabromonorbornyl derivatives.

3) A short and efficient route to novel, unexplored structural motifs, viz, 7-azaspiro[4.5]decan-6-ones from norbornyl derivatives was developed by following a useful new sequence of reactions involving radical mediated bridgehead C-C bond formation of the potential bridged bicyclic lactones.

Chart 17: cyclopentanoids from  $\alpha$ -diketones



4) The  $\alpha$ -diketones were cleverly designed to provide a short synthetic access to  $\gamma$ - and  $\delta$ - lactones; an elegant and stereoselective strategy for a rigid DAG model was developed and an advance intermediate for its synthesis was prepared in just 3 steps starting from tetrachloro cyclopentadiene adduct.

The establishment of an elegant and stereoselective strategy to replace the 1,2-dihaloalkene bridge by the oxygen bridge via the  $\alpha$ -diketones, paves the way to design and prepare few interesting rigid molecular scaffolds; which could act as smart molecules upon suitable elaboration, is the contents of **Chapter 2**. A beautiful orchestration of selective utilization of the two sets of chlorines along with an illustration of an unprecedented example of extracting fullest advantage of geometric constraints on the reactivity of the molecule was demonstrated. In contrast to all the applications known so far of tetrachloro norbornyl derivatives where complete dechlorination is invariably followed, the availability of 'retained' bridgehead chlorines by our method, facilitate smooth incorporation of oxa-bridges in a stepwise manner through a formal 'bisnucleophilic' oxygen. The *endo-anti-endo*-bis-adducts of tetrachlorocyclopentadiene with cyclopentadiene and furan furnished the corresponding oxa-bridged compounds and could serve as perspective building blocks for *cis:anti:cis* triquinanes and oxatriquinanes. Bicyclo [3.3.0] octane and [5.3.0] decane derivatives were conveniently accessed by alkaline cleavage of the diketones.

The section A of **Chapter 3** described a novel, efficient and regio- as well as diastereoselective conversion of non-enolizable bicyclic  $\alpha$ -diketones into synthetically useful acyloins mediated by indium metal, tolerable to a variety of sensitive substituents such as acetate, ester and bridgehead halogens (Chart 19). Further the methodology was extended to the synthesis of highly functionalized

cyclopentane carboxaldehydes, potential building blocks in organic syntheses via cleavage of the acyloins under  $\text{Pb}(\text{OAc})_4/\text{MeOH-PhH}$  conditions. The allylindium addition was performed with carboxaldehydes, which were found to be highly diastereoselective. There was reversal in the selectivity in going from ethoxy derivative to phenyl derivative perhaps due to chelation control in the case of former.

Chart 18: Synthesis of novel oxa-bridged derivatives

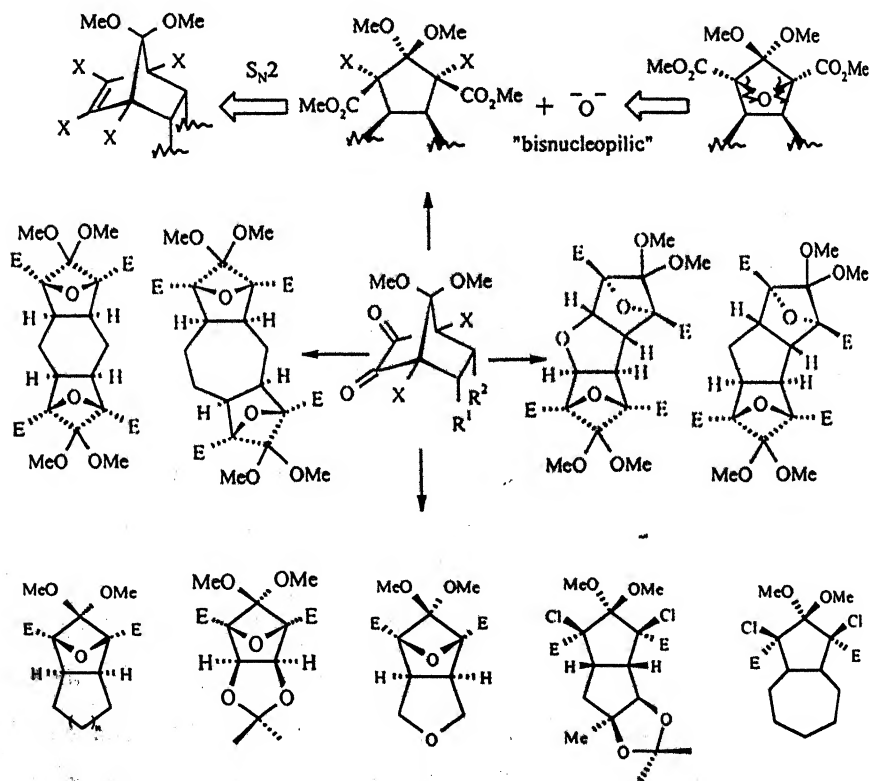
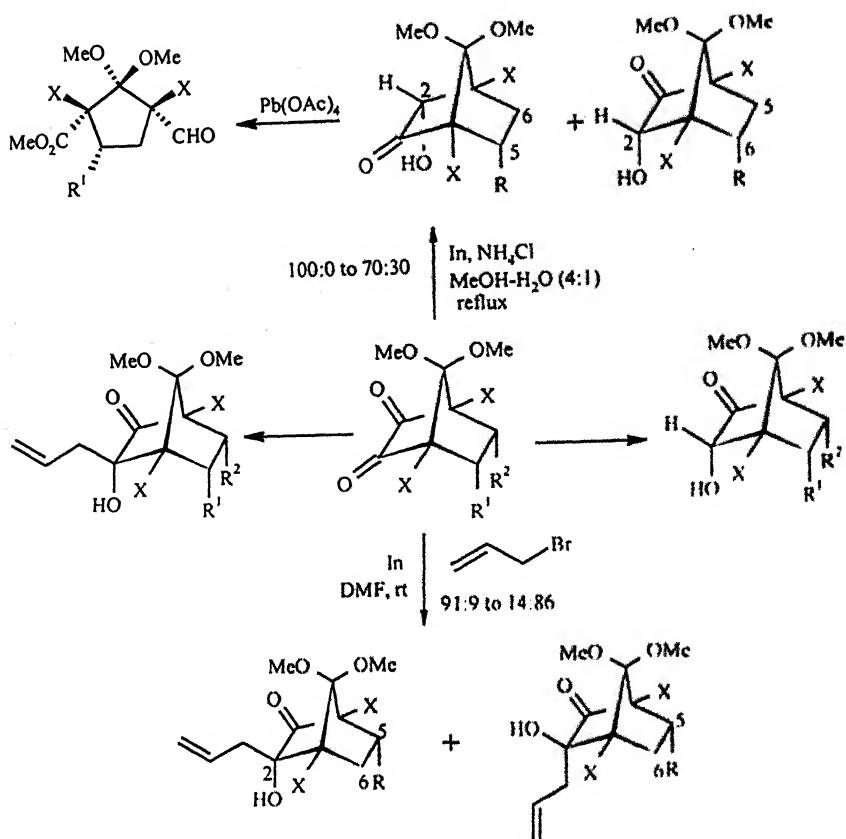


Chart 19: Indium mediated reactions of  $\alpha$ -diketones

Unlike the indium mediated reductions, where the reduction of the  $\alpha$ -diketone was taking place, formally, either to the carbon present in the same side or opposite side of the *endo* substituent, the coupling of the allylindium reagent was highly regioselective; the reagent added exclusively to the carbonyl group, diagonal to the *endo* substituent (Chart 19). The present study in **Chapter 3B** demonstrates the highly

diastereoselective addition of allylindium to norbornyl  $\alpha$ -diketones. In case of monosubstituted derivatives also, a complete reversal in the diastereoselection was observed when the *endo*-substituent was changed to *endo*-oxygenated group attached to norbornyl through oxygen.

## Experimental Section

### General information

All the reactions were performed in oven dried apparatus and the reaction mixtures were magnetically stirred. Thin layer chromatography was performed on Acme Silica gel (Mumbai, India) coated on microscopic slides. Visualization of spots was effected by exposure to iodine or spraying with 10% methanolic  $\text{H}_2\text{SO}_4$  and charring. Column chromatography was performed using Acme's silica gel (100-200 mesh), and ethyl acetate-hexane was used as eluent. Evaporation of solvents were performed at reduced pressure, using a Buchi rotary evaporator.

Melting points are uncorrected and were recorded on JSGW melting point apparatus. Infrared spectra were recorded on Perkin-Elmer 1320 and Shimadzu 420 spectrophotometers as KBr pellets (solids), or as thin films on NaCl flats (liquids).  $^1\text{H}$  NMR was recorded at 400 MHz on JEOL spectrophotometer unless otherwise mentioned (500 MHz, 300 MHz, 80 MHz, 60 MHz). Data are reported as follows: (br=broad, s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet; integration; coupling constant(s) in Hz; assignment). Chemical shifts are reported in ppm, and coupling constants are reported in Hz. Proton decoupled  $^{13}\text{C}$  NMR spectra were recorded at 100 MHz on JEOL spectrophotometer unless otherwise mentioned (125 MHz). DEPT were recorded at  $135^\circ$  angle and represented as  $\text{CH}_3$ ,  $\text{CH}_2$ ,  $\text{CH}$  and  $\text{Cq}$  (quarternary). Samples for NMR were made in  $\text{CDCl}_3$  and insoluble

compounds were made to dissolve by adding additional 3-4 drops of DMSO- $d_6$  into the  $CDCl_3$  solution. Tetramethylsilane was used as the internal standard. CHN analysis was done in Technische Universität Dresden, Sektion Chemie.

Commercial grade solvents were distilled before use. Hexane used was the fraction between 60-80 °C. Ethyl acetate was distilled over anhydrous potassium carbonate. Dichloromethane and chloroform were distilled over phosphorous pentoxide and stored over 4 Å molecular sieves. Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl under nitrogen. Benzene was refluxed and dried over sodium. Acetic anhydride was distilled prior to use. Pyridine was distilled and stored over potassium hydroxide pellets. Dimethyl formamide (DMF) was purified by forming benzene-water azeotrope, distilling it under vacuum and storing over 4Å molecular sieves. Methanol and ethanol were refluxed and distilled over magnesium turnings and stored over 4 Å molecular sieves. Acetonitrile was distilled over  $P_2O_5$ . Distilled water was used for aqueous reactions.

Tributyltin hydride was purchased from Aldrich, and was also prepared from tributyltin chloride and  $LiAlH_4$  following literature procedure.<sup>97</sup>  $RuCl_3 \cdot 3H_2O$  was purchased from Arora Mathey Company. Indium,  $Pb(OAc)_4$ , and  $NaIO_4$  were purchased from Spectrochem India limited.

## Chapter 1A

### Synthetic Studies Towards Pentenomycins

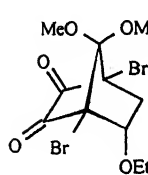
**General procedure for the synthesis of  $\alpha$ -diketones:**<sup>1</sup> To a vigorously stirred solution of the substrate (0.5 mmol) in acetonitrile (6 ml) at 0–5°C (ice-water bath) was added a solution of  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$  (0.035 mmol) and  $\text{NaIO}_4$  (0.75 mmol) in water (1 ml). The mixture was stirred for the specified time and continuously monitored by tlc. The resulting suspension was filtered through a thin pad of silica gel, which was then washed with ethyl acetate (15 ml). Concentration of the filtrate followed by silica gel column chromatography gave the pure yellow colored diketones.

**General procedure for the cleavage of  $\alpha$ -diketones:**<sup>1</sup> To a stirred solution of diketone (1 mmol) in methanol (5 ml) was added 30%  $\text{H}_2\text{O}_2$  (0.75 ml) followed by slow addition of 6N  $\text{NaOH}$  solution (0.3 ml). After stirring at room temperature ( $\sim 20^\circ\text{C}$ ) for 1–3 hrs, 5%  $\text{HCl}$  (10 ml) was added and extracted with ethyl acetate (3 $\times$ 5 ml). The combined ethyl acetate layer was washed once with brine and dried over  $\text{Na}_2\text{SO}_4$ . The crude carboxylic acid obtained after concentration of ethyl acetate layer was treated with excess diazomethane in ether:methanol (1:1) at 0°C. After quenching excess diazomethane with acetic acid, the solution was concentrated and silica gel column chromatography afforded the pure products.



**1,4-Dibromo-5-ethoxy-7,7-dimethoxy-bicyclo[2.2.1]heptane-2,3-**

**dione 2b:** Yield: 96%, yellow solid; mp 72-78 °C;  $^1\text{H}$  NMR  $\delta$  4.33 (dd, 1H,  $J = 9.5, 2.2$  Hz, C(5) $\text{H}_{\text{exo}}$ ), 3.76 (s, 3H, OMe), 3.69-3.63 (m, 1H,

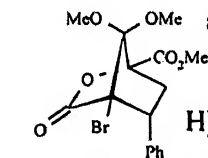


CH<sub>2</sub>), 3.60 (s, 3H, OMe), 3.57-3.51 (m, 1H, CH<sub>2</sub>), 3.01 (dd, 1H,  $J = 13.5, 9.5$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.19 (dd, 1H,  $J = 13.5, 2.2$  Hz, C(6) $\text{H}_{\text{endo}}$ ), 1.12 (t, 3H,  $J = 6.8$  Hz, Me),

$^{13}\text{C}$  NMR  $\delta$  187.2 (-C=O), 184.6 (-C=O), 102.6, 80.9, 72.7, 66.8, 66.3, 52.8 (OMe), 52.1 (OMe), 42.5, 14.9 (Me); IR (KBr): 2900, 1770, 1440, 1330  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{11}\text{H}_{14}\text{Br}_2\text{O}_5$ : C 34.22, H 3.66; Found: C 34.13, H 3.69.

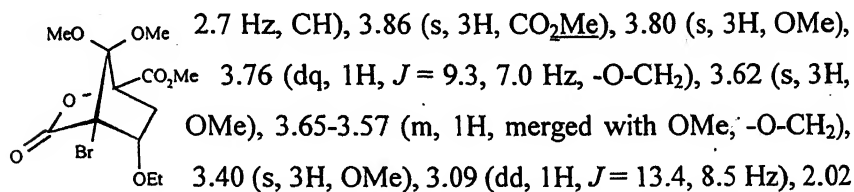
**4-Bromo-7,7-dimethoxy-3-oxo-5-phenyl-2-oxa-**

**bicyclo[2.2.1]heptane-1-carboxylic acid methyl ester 52a:** Yield: 72%, colorless solid, mp 149-151 °C,  $^1\text{H}$  NMR  $\delta$  7.36-7.29 (m, 3H,

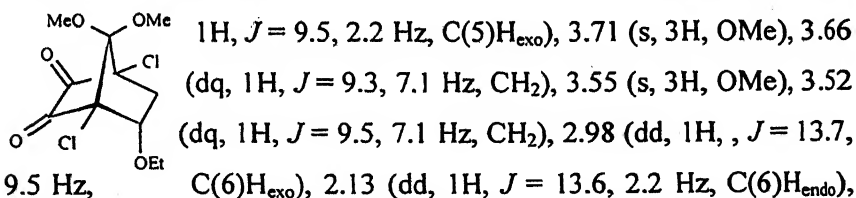


aromatic), 7.23-7.20 (m, 2H, aromatic), 3.91 (s, 3H, CO<sub>2</sub>Me), 3.82 (dd, 1H,  $J = 10.8, 4.9$  Hz, benzylic H), 3.74 (s, 3H, OMe), 3.45 (s, 3H, OMe), 3.24 (dd, 1H,  $J = 13.7, 10.8$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.45 (dd, 1H,  $J = 13.7, 5.1$  Hz, C(6) $\text{H}_{\text{endo}}$ );  $^{13}\text{C}$  NMR  $\delta$  166.7 (O-C=O), 166.1 (O-C=O), 135.4, 128.7 (CH), 128.6 (CH), 128.3 (CH), 109.6, 84.9, 70.1, 53.3 (CH<sub>3</sub>), 52.0 (CH<sub>3</sub>), 51.7 (CH<sub>3</sub>), 46.9 (CH), 39.3 (CH<sub>2</sub>); IR (KBr) 2900, 1790, 1740,

1590, 1430, 1170, 700  $\text{cm}^{-1}$ . Anal. Calcd. for  $\text{C}_{16}\text{H}_{16}\text{BrO}_6$ : C, 50.02; H, 4.20. Found: C, 49.60; H, 4.40.

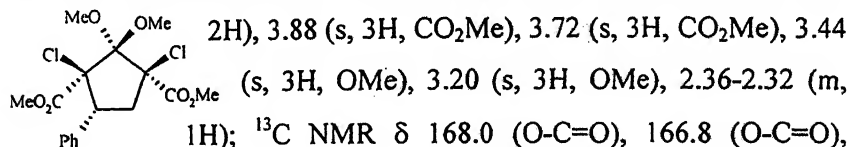
**4-Bromo-5-ethoxy-7,7-dimethoxy-3-oxo-2-oxa-****bicyclo[2.2.1]heptane-1-carboxylic acid methyl ester 52b:** Yield:78%; colorless solid; mp 96-98 °C;  $^1\text{H}$  NMR  $\delta$  4.30 (dd, 1H,  $J = 8.5$ ,

(dd, 1H,  $J = 13.4, 8.5$  Hz), 1.18 (t, 3H,  $J = 7.0$  Hz, Me),  $^{13}\text{C}$  NMR  $\delta$   
 166.8 ( $\text{O}-\text{C}=\text{O}$ ), 165.4 ( $\text{O}-\text{C}=\text{O}$ ), 108.8, 84.9, 78.7, 67.8, 66.8, 53.2  
 ( $\text{CO}_2\text{Me}$ ), 51.67 (OMe), 51.65 (OMe), 40.3, 15.1 (Me); IR (KBr): 2850,  
 1780, 1720, 1420,; Anal. calcd. for  $\text{C}_{12}\text{H}_{17}\text{BrO}_7$ : C 40.81, H 4.85;  
 Found: C 40.90, H 4.89.

**1,4-Dichloro-5-ethoxy-7,7-dimethoxy-bicyclo[2.2.1]heptane-2,3-****dione 1b:** Yield: 98%, yellow solid; mp 47-49 °C;  $^1\text{H}$  NMR  $\delta$  4.28 (dd,

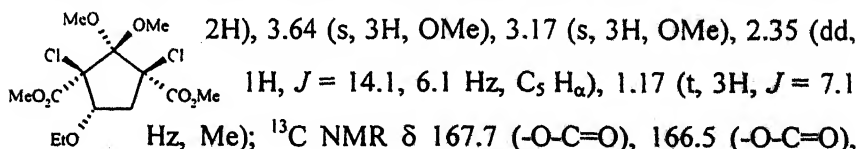
1.13 (t, 3H,  $J = 7.1$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  187.2 ( $-\text{C}=\text{O}$ ), 185.5 ( $-\text{C}=\text{O}$ ),  
 102.6, 80.8, 79.4, 74.5, 66.8, 52.6 (OMe), 52.1 (OMe), 41.0, 14.9 (Me);  
 IR (KBr): 2850, 1760, 1440, 1330  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{O}_5$ : C  
 44.47, H 4.75; Found: C 44.51, H 4.77.

**1,3-Dichloro-2,2-dimethoxy-4-phenyl-cyclopentane-1,3-dicarboxylic acid dimethyl ester 50a:** Yield: 93%; mp 87-88 °C, colourless solid (dichloromethane/hexane),  $^1\text{H}$  NMR  $\delta$  7.40-7.28 (m, 5H), 4.10-3.97 (m,



135.2, 128.2 (CH), 128.0 (CH), 127.8 (CH), 110.5, 81.8, 77.5, 53.5 ( $\text{CH}_3$ ), 53.3 ( $\text{CH}_3$ ), 53.2 ( $\text{CH}_3$ ), 52.9 ( $\text{CH}_3$ ), 52.1 (CH), 40.8 ( $\text{CH}_2$ ); IR (KBr) 2900, 1710, 1410, 1200, 900  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{17}\text{H}_{20}\text{Cl}_2\text{O}_6$ : C, 52.19; H, 5.15. Found: C, 52.18; H, 5.13.

**1,3-Dichloro-4-ethoxy-2,2-dimethoxy-cyclopentane-1,3-dicarboxylic acid dimethyl ester 50b:** Yield: 81%; colorless solid, mp 62-64 °C;  $^1\text{H}$  NMR  $\delta$  4.38 (dd, 1H,  $J = 12.2, 6.1$  Hz,  $\text{C}_4 \text{H}_\beta$ ), 3.84 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.84-3.80 (m, 1H, buried under OMe), 3.67-3.56 (m,



108.5 ( $\text{C}_2$ ), 86.5 ( $\text{C}_4$ ), 80.4, 76.5, 67.3, 53.5, 53.4, 52.9, 52.2, 42.4, 15.4; IR (KBr) 2850, 1740, 1430, 1220, 1060  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{13}\text{H}_{20}\text{Cl}_2\text{O}_6$ : C, 45.50; H, 5.87. Found: C, 45.46; H, 5.88.

**4-Chloro-7,7-dimethoxy-3-oxo-5-phenyl-2-oxa-****bicyclo[2.2.1]heptane-1-carboxylic acid methyl ester 51a:** Yield:

81%, colorless solid, mp 140-142 °C,  $^1\text{H}$  NMR  $\delta$  7.35-7.21 (m, 5H, aromatic), 3.91 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.78 (dd, 1H,  $J = 11.0$ , 5.1 Hz, benzylic H), 3.71 (s, 3H, OMe), 3.45 (s, 3H, OMe), 3.23 (dd, 1H,  $J = 13.9$ , 10.9 Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.42 (dd, 1H,  $J = 13.9$ , 5.1 Hz, C(6) $\text{H}_{\text{endo}}$ );  $^{13}\text{C}$  NMR  $\delta$  166.8 (O-C=O), 166.1 (O-C=O), 135.2, 128.6, 128.4, 109.4, 84.6 ( $\text{C}_1$ ), 77.7 ( $\text{C}_4$ ), 53.3 (OMe), 52.0 (OMe), 51.7 (OMe), 46.9, 39.3; IR (KBr) 2850, 1790, 1740, 1590, 1420, 710  $\text{cm}^{-1}$ . Anal. Calcd. for  $\text{C}_{16}\text{H}_{16}\text{ClO}_6$ : C, 56.56; H, 4.75. Found: C, 56.58; H, 4.77.

**4-Chloro-5-ethoxy-7,7-dimethoxy-3-oxo-2-oxa-****bicyclo[2.2.1]heptane-1-carboxylic acid methyl ester 51b:** Yield:

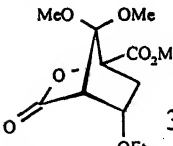
73%; colorless solid; mp 86-88 °C;  $^1\text{H}$  NMR  $\delta$  4.28 (dd, 1H,  $J = 8.6$ , 2.6 Hz, C(5) $\text{H}_{\text{exo}}$ ), 3.86 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.77 (dq, 1H,  $J = 9.5$ , 7.1 Hz, -O-CH<sub>2</sub>), 3.63-3.55 (m, 1H, merged with OMe, -O-CH<sub>2</sub>), 3.58 (s, 3H, OMe), 3.40 (s, 3H, OMe), 3.10 (dd, 1H,  $J = 13.7$ , 8.6 Hz), 2.00 (dd, 1H,  $J = 13.7$ , 2.6 Hz), 1.18 (t, 3H,  $J = 7.0$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  165.8 (O-C=O), 165.6 (O-C=O), 108.7, 84.9 ( $\text{C}_1$ ), 78.3 ( $\text{C}_4$ ), 66.9, 53.3, 51.8, 51.6, 39.7, 15.2 (Me); IR (KBr): 2950, 1800, 1740, 1440, 1310; Anal. calcd. for  $\text{C}_{12}\text{H}_{17}\text{ClO}_7$ : C 46.69, H 5.55; Found: C 46.72, H 5.57.

**General Procedure for bridgehead reduction:** A solution of the bromo lactone (0.5 mmol),  $\text{Bu}_3\text{SnH}$  (0.6 mmol) and AIBN (0.012 mmol, 5 mol%) in benzene (3 ml) was refluxed under an inert atmosphere. After completion of the starting material (tlc monitoring), benzene was distilled off in a rotavapor. The crude reaction mixture was directly purified by silica gel column chromatography. First 50 ml fractions were collected with hexane as eluent to remove tin impurities and later on polarity of the eluent (EtOAc-hexane) was increased to get the pure product.

**7,7-Dimethoxy-3-oxo-5-phenyl-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid methyl ester 55a:** Yield: 91%; colourless solid

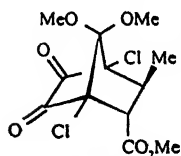
(EtOAc/hexane); mp 120-122 °C;  $^1\text{H}$  NMR  $\delta$  7.33-7.20 (m, 5H, aromatic), 3.88 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.85-3.80 (m, 1H, benzylic H), 3.46 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.21 (d, 1H,  $J=4.2$  Hz, bridgehead H), 3.13 (dd, 1H,  $J=13.7$ , 10.5 Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 2.33 (dd, 1H,  $J=13.7$ , 5.2 Hz,  $\text{C}(6)\text{H}_{\text{endo}}$ );  $^{13}\text{C}$  NMR  $\delta$  170.1 (O-C=O), 166.8 (O-C=O), 138.3, 128.7, 127.5, 127.4, 111.9, 87.0, 55.7, 53.0, 51.5, 51.4, 38.6, 38.5; IR (KBr): 2850, 1790, 1720, 1420, 1320, 1260, 1000, 940  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{16}\text{H}_{18}\text{O}_6$ : C 62.74, H 5.92; Found: C 62.71, H 5.90.

**5-Ethoxy-7,7-dimethoxy-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid methyl ester 55b:** Yield: 93%; colorless solid

(EtOAc/hexane); mp 92-94 °C,  $^1\text{H}$  NMR  $\delta$  4.29-4.25 (m, 1H,  $\text{H}_{\text{exo}}$ ),  

 $3.81$  (s, 3H,  $\text{CO}_2\text{Me}$ ),  $3.52$  (dq, 1H,  $J = 8.8, 7.0$  Hz, -O-  
 $\text{CH}_2$ ),  $3.43$ - $3.34$  (m, 1H, merged with bridgehead H),  
 $3.37$  (d, 1H,  $J = 4.2$  Hz, bridgehead H),  $3.30$  (s, 3H,  
 OMe),  $3.23$  (s, 3H, OMe),  $2.94$  (dd, 1H,  $J = 13.7, 8.5$  Hz,  $\text{H}_{\text{exo}}$ ),  $1.91$   
 (dd, 1H,  $J = 13.7, 2.5$  Hz,  $\text{H}_{\text{endo}}$ ),  $1.12$  (t, 3H,  $J = 7.0$  Hz, Me),  $^{13}\text{C}$  NMR  
 $\delta$  168.7 (O-C=O), 166.6 (O-C=O), 111.5, 86.8, 72.7, 64.8, 53.6, 53.0,  
 51.4, 51.3, 39.7, 14.9 (Me); IR (KBr): 2900, 1770, 1740, 1430, 1270  
 $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{12}\text{H}_{18}\text{O}_7$ : C 52.55, H 6.61; Found: C 52.53, H  
 6.63.

**1,4-Dichloro-7,7-dimethoxy-3-methyl-5,6-dioxo-**

**bicyclo[2.2.1]heptane-2-carboxylic acid methyl ester 57:** Yield: 94%,  
 yellow solid (dichloromethane/hexane); mp 89 °C;  $^1\text{H}$  NMR  $\delta$  3.74 (s,  
 3H, OMe), 3.73 (s, 3H, OMe), 3.54 (s, 3H, OMe), 3.16 (d, 1H,  $J = 6.3$



Hz, C(3) $\text{H}_{\text{exo}}$ ), 2.41 (qn, 1H,  $J = 6.8$  Hz, C(3) $\text{H}_{\text{endo}}$ ), 1.48  
 (d, 3H,  $J = 6.8$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  186.9 (-C=O),  
 186.0 (-C=O), 170.0, 102.5, 77.6, 77.5, 56.4 (OMe),  
 53.0 (OMe), 52.3 (OMe), 51.8, 39.1, 17.2 (Me); IR (KBr): 2900, 1760,  
 1720, 1420, 1340, 1260, 1190  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{12}\text{H}_{14}\text{Cl}_2\text{O}_6$ : C  
 44.33, H 4.34; Found: C 44.36, H 4.35.

**1,4-Dichloro-5,5-dimethoxy-3-methyl-cyclopentane-1,2,4-**

**tricarboxylic acid trimethyl ester 58:** Yield: 89%, white solid

(dichloromethane/hexane); mp 87 °C;  $^1\text{H}$  NMR  $\delta$  3.84 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.45-3.38 (m, 1H), 3.35-3.32 (m, 1H), 3.25 (s, 3H, OMe), 1.25 (d, 3H,  $J$  = 6.8 Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  169.8 (-O-C=O), 167.6 (-O-C=O), 167.6 (-O-C=O), 110.4, 79.6, 77.7, 53.5, 53.3, 51.1, 51.9, 51.7, 41.3, 13.5 (Me); IR (KBr): 2900, 1740, 1410, 1270, 1230, 1010  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{14}\text{H}_{20}\text{Cl}_2\text{O}_8$ : C 43.43, H 5.21; Found: C 43.46, H 5.23.

**1,2,3,4-Tetrachloro-7,7-dimethoxy-5-methyl-5-phenyl-**

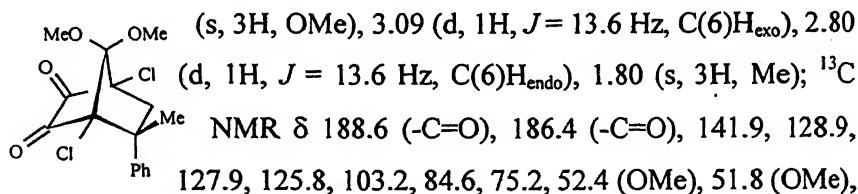
**bicyclo[2.2.1]hept-2-ene 59:** Yield: 81%, obtained as yellow viscous liquid;  $^1\text{H}$  NMR  $\delta$  7.29-7.25 (m, 5H, aromatic), 3.68 (s, 3H, OMe), 3.54 (s, 3H, OMe), 2.94 (d, 1H,  $J$  = 12.4 Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.51 (d, 1H,  $J$  = 12.4 Hz, C(6) $\text{H}_{\text{endo}}$ ), 1.81 (s, 3H, Me); IR (KBr): 2900, 1600, 1480, 1440, 1370, 1280, 1200  $\text{cm}^{-1}$ .

**1,2,3,4-Tetrabromo-7,7-dimethoxy-5-methyl-5-phenyl-**

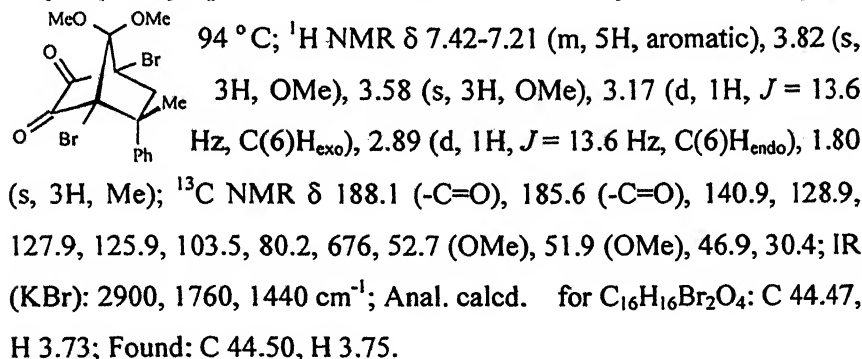
**bicyclo[2.2.1]hept-2-ene 60:** Yield: 79%, colorless solid; mp 84 °C;  $^1\text{H}$  NMR  $\delta$  7.97-7.20 (m, 5H, aromatic), 3.70 (s, 3H, OMe), 3.57 (s, 3H, OMe), 3.02 (d, 1H,  $J$  = 12.5 Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.56 (d, 1H,  $J$  = 12.6 Hz, C(6) $\text{H}_{\text{endo}}$ ), 1.81 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  141.8, 129.6, 128.0, 127.4, 126.8, 103.5, 80.2, 68.6, 52.9 (OMe), 52.0 (OMe), 51.5, 47.5, 30.4; IR (KBr): 2900, 1560, 1480, 1430, 1360  $\text{cm}^{-1}$ .

**1,4-Dichloro-7,7-dimethoxy-5-methyl-5-phenyl-**

**bicyclo[2.2.1]heptane-2,3-dione 61:** Yield: 91%, yellow solid; mp 59-61 °C;  $^1\text{H}$  NMR  $\delta$  7.28-7.21 (m, 5H, aromatic), 3.78 (s, 3H, OMe), 3.54

**1,4-Dibromo-7,7-dimethoxy-5-methyl-5-phenyl-**

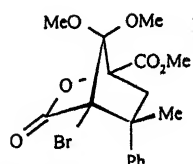
**bicyclo[2.2.1]heptane-2,3-dione 62:** Yield: 87%, yellow solid; mp 92-94 °C;  $^1\text{H}$  NMR  $\delta$  7.42-7.21 (m, 5H, aromatic), 3.82 (s,

**4-Bromo-7,7-dimethoxy-5-methyl-3-oxo-5-phenyl-2-oxa-**

**bicyclo[2.2.1]heptane-1-carboxylic acid methyl ester 63:** Yield: 83%, colorless solid (dichloromethane/hexane); mp 135-136 °C;  $^1\text{H}$  NMR  $\delta$  7.71-7.22 (m, 5H, aromatic), 3.89 (s, 3H, OMe), 3.71 (s, 3H, OMe),

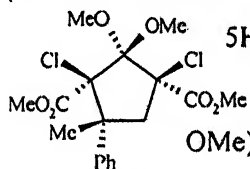


3.39 (s, 3H, OMe), 3.14 (d, 1H,  $J = 14.0$  Hz, C(6)H<sub>exo</sub>), 3.01 (d, 1H,  $J =$



14.0 Hz, C(6)H<sub>endo</sub>), 1.86 (s, 3H, Me); <sup>13</sup>C NMR  $\delta$  166.9 (-O-C=O), 166.3 (-O-C=O), 142.4, 128.3, 127.5, 126.8, 109.4, 84.9 (C<sub>1</sub>), 75.6 (C<sub>4</sub>), 53.2 (OMe), 51.7 (OMe), 51.6 (OMe), 45.7 (C<sub>5</sub>), 44.6 (C<sub>6</sub>), 26.8 (Me); IR (KBr): 2900, 1790, 1720, 1610, 1420 cm<sup>-1</sup>, Anal. Calcd. for C<sub>17</sub>H<sub>18</sub>BrO<sub>6</sub>: C 51.27, H 4.56; Found: C 51.31, H 4.54.

**1,3-Dichloro-2,2-dimethoxy-4-methyl-4-phenyl-cyclopentane-1,3-dicarboxylic acid dimethyl ester 64:** Yield: 61%, colorless solid (dichloromethane/hexane); mp 99-100 °C; <sup>1</sup>H NMR  $\delta$  7.51-7.20 (m,



5H, aromatic), 4.64 (d, 1H,  $J = 14.0$  Hz), 3.83 (s, 3H, OMe), 3.74 (s, 3H, OMe), 3.28 (s, 3H, OMe), 3.27 (s, 3H, OMe), 1.74 (s, 3H, Me); <sup>13</sup>C NMR  $\delta$  168.4 (-O-C=O), 167.7 (-O-C=O), 144.8, 128.2, 126.9, 125.6, 111.4, 88.6, 77.6, 53.4, 53.3, 53.0, 45.7 (C<sub>5</sub>), 44.6 (C<sub>6</sub>), 26.8 (Me); IR (KBr): 2900, 1720, 1600, 1500, 1440, 1390, 1220, 1080 cm<sup>-1</sup>; Anal. calcd. for C<sub>11</sub>H<sub>22</sub>Cl<sub>2</sub>O<sub>6</sub>: C 41.13, H 6.90; Found: C 41.17, H 6.93.

**4-Chloro-7,7-dimethoxy-5-methyl-3-oxo-5-phenyl-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid methyl ester 65:** Yield: 14%, colorless solid (dichloromethane/hexane); mp 108-110 °C; <sup>1</sup>H NMR  $\delta$  7.45-7.21 (m, 5H, aromatic), 3.90 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.39 (s, 3H, OMe), 3.11 (d, 1H,  $J = 13.9$  Hz, C(6)H<sub>exo</sub>), 2.98 (d, 1H,  $J =$

14.0 Hz, C(6) $H_{\text{endo}}$ ), 1.80 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  167.0 (-O-C=O), 167.2 (-O-C=O), 142.3, 128.4, 127.5, 126.9, 109.2, 84.2 ( $\text{C}_1$ ), 80.9 ( $\text{C}_4$ ), 53.2 (OMe), 51.7 (OMe), 51.5 (OMe), 45.8 ( $\text{C}_5$ ), 44.1 ( $\text{C}_6$ ), 25.8 (Me); IR (KBr): 2900, 1800, 1740, 1590, 1440, 1300, 1240  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{17}\text{H}_{18}\text{ClO}_6$ : C 57.72, H 5.13; Found: C 57.76, H 5.14.

**1,4,5,6-Tetrabromo-7,7-dimethoxy-2-methyl-bicyclo[2.2.1]hept-5-ene-2-carboxylic acid methyl ester 67:** Yield: 91%, colorless solid (dichloromethane/hexane); mp 142-144  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  3.68 (s, 3H,

OMe), 3.63 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.02 (d, 1H,  $J = 11.9$  Hz, C(3) $H_{\text{exo}}$ ), 2.26 (d, 1H,  $J = 12.6$  Hz, C(3) $H_{\text{endo}}$ ), 1.62 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  172.5 (-O-C=O), 126.8, 126.1, 112.3, 74.9, 67.7, 55.2 ( $\text{C}_2$ ), 53.1 (OMe), 52.5 (OMe), 51.6 (OMe), 45.6, 22.3 (Me); IR (KBr): 2900, 1730, 1560, 1440, 1380  $\text{cm}^{-1}$ .

**1,4-Dichloro-7,7-dimethoxy-2-methyl-5,6-dioxo-**

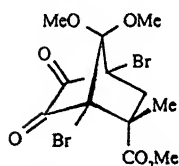
**bicyclo[2.2.1]heptane-2-carboxylic acid methyl ester 68:** Yield: 57%, yellow viscous liquid;  $^1\text{H}$  NMR  $\delta$  3.72 (s, 3H, OMe), 3.65 (s, 3H,

OMe), 3.53 (s, 3H, OMe), 2.86 (d, 1H,  $J = 13.2$  Hz, C(3) $H_{\text{exo}}$ ), 2.50 (d, 1H,  $J = 13.2$  Hz, C(3) $H_{\text{endo}}$ ), 1.67 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  187.4 (-C=O), 186.4 (-C=O), 172.7 (-O-C=O), 102.8 ( $\text{C}_7$ ), 81.9, 74.3, 53.3 (OMe), 52.5 (OMe), 51.8

(OMe), 51.0 (C<sub>2</sub>), 43.9(C<sub>3</sub>), 21.3 (Me); IR (neat): 2900, 1760, 1720, 1430, 1360 cm<sup>-1</sup>; Anal. calcd. for C<sub>12</sub>H<sub>14</sub>Cl<sub>2</sub>O<sub>6</sub>: C 44.33, H 4.34; Found: C 44.35, H 4.37.

**1,4-Dibromo-7,7-dimethoxy-2-methyl-5,6-dioxo-**

**bicyclo[2.2.1]heptane-2-carboxylic acid methyl ester 69:** Yield: 54%,

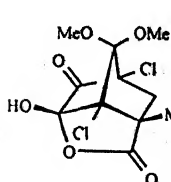


yellow solid (dichloromethane/hexane); mp 96-98 °C; <sup>1</sup>H NMR δ 3.76 (s, 3H, OMe), 3.65 (s, 3H, OMe), 3.58 (s, 3H, OMe), 2.92 (d, 1H, *J* = 13.2 Hz, C(3)H<sub>exo</sub>), 2.60 (d, 1H, *J* = 13.2 Hz, C(3)H<sub>endo</sub>), 1.71 (s, 3H, Me); <sup>13</sup>C NMR δ 186.7

(-C=O), 185.5 (-C=O), 172.7 (-O-C=O), 103.0 (C<sub>7</sub>), 76.5, 66.4, 53.2 (OMe), 52.7 (OMe), 52.0 (C<sub>2</sub>), 45.3 (C<sub>3</sub>), 26.3 (Me); IR (neat): 2900, 1760, 1720, 1360 cm<sup>-1</sup>; Anal. calcd. for C<sub>12</sub>H<sub>14</sub>Br<sub>2</sub>O<sub>6</sub>: C 34.81, H 3.41; Found: C 34.84, H 3.44.

**1,7-Dichloro-3-hydroxy-8,8-dimethoxy-6-methyl-4-oxa-**

**tricyclo[4.2.1.0<sup>3,7</sup>]nonane-2,5-dione 70:** Yield: 35%, colorless solid



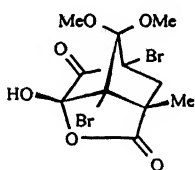
(EtOAc); mp 152-154 °C; <sup>1</sup>H NMR (CDCl<sub>3</sub>:DMSO, 20:1) δ 4.50 (br s, 1H, OH, D<sub>2</sub>O exchangeable), 3.69 (s, 3H, OMe), 3.63 (s, 3H, OMe), 2.54 (d, 1H, *J* = 13.4 Hz, C(8)H<sub>exo</sub>), 2.48 (d, 1H, *J* = 13.4 Hz, C(8)H<sub>endo</sub>), 1.54

(s, 3H, Me); <sup>13</sup>C NMR δ 192.7 (-C=O), 173.2 (-O-C=O), 102.5 (C<sub>8</sub>), 102.5 (C<sub>3</sub>), 78.4, 73.9, 52.5 (OMe), 51.7 (OMe), 51.6 (C<sub>6</sub>), 41.3 (C<sub>8</sub>),

17.8 (Me); IR (KBr): 3150, 2900, 1760 (br), 1430, 1370  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{11}\text{H}_{12}\text{Cl}_2\text{O}_6$ : C 42.47, H 3.89; Found: C 42.51, H 3.91.

**1,7-Dibromo-3-hydroxy-8,8-dimethoxy-6-methyl-4-oxa-**

**tricyclo[4.2.1.0<sup>3,7</sup>]nonane-2,5-dione 71:** Yield: 33%, colorless solid (EtOAc); mp 188-190 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ :DMSO, 20:1)  $\delta$  3.71 (s, 3H, OMe), 3.67 (s, 3H, OMe), 2.58 (d, 1H,  $J = 13.2$  Hz, C(8) $\text{H}_{\text{exo}}$ ), 2.47

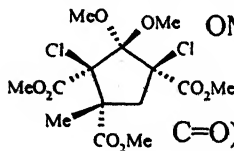


(d, 1H,  $J = 13.4$  Hz, C(8) $\text{H}_{\text{endo}}$ ), 1.54 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  193.4 ( $-\text{C}=\text{O}$ ), 173.8 ( $-\text{O}-\text{C}=\text{O}$ ), 102.5 ( $\text{C}_8$ ), 101.1 ( $\text{C}_3$ ), 72.7, 66.6, 52.6 (OMe), 52.5 (OMe), 51.5 ( $\text{C}_6$ ), 44.2 ( $\text{C}_8$ ), 20.1 (Me); IR (KBr): 3150, 2900,

1760 (br), 1430  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{11}\text{H}_{12}\text{Br}_2\text{O}_6$ : C 33.03, H 3.02; Found: C 33.07, H 3.01.

**2,4-Dichloro-3,3-dimethoxy-1-methyl-cyclopentane-1,2,4-**

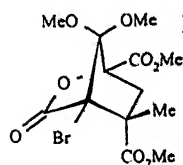
**tricarboxylic acid trimethyl ester 72:** Yield: 78%; colorless solid, mp 54 °C;  $^1\text{H}$  NMR  $\delta$  4.30 (d, 1H,  $J = 15.5$  Hz,  $\text{C}_5\text{H}_\beta$ ), 3.79 (s, 3H, OMe), 3.77 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.43 (s, 3H,



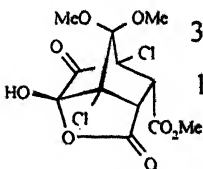
OMe), 2.38 (d, 1H,  $J = 15.5$  Hz,  $\text{C}_5\text{H}_\alpha$ ), 1.65 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  173.9 ( $-\text{O}-\text{C}=\text{O}$ ), 168.7 ( $-\text{O}-\text{C}=\text{O}$ ), 168.7 ( $-\text{O}-\text{C}=\text{O}$ ), 110.4 ( $\text{C}_2$ ), 82.2, 75.6, 54.6 ( $\text{C}_4$ ), 53.8 (OMe), 53.3 (OMe), 53.2 (OMe), 52.4 (OMe), 47.0 ( $\text{C}_5$ ), 24.7 (Me); IR (KBr) 2900, 1720, 1420, 1320  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{14}\text{H}_{20}\text{Cl}_2\text{O}_8$ : C 43.43, H 5.21; Found: C 43.48, H 5.24.

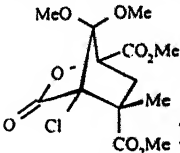
**4-Bromo-7,7-dimethoxy-5-methyl-3-oxo-2-oxa-****bicyclo[2.2.1]heptane-1,5-dicarboxylic acid dimethyl ester 73:**

Yield: 92%; colorless solid, mp 110 °C;  $^1\text{H}$  NMR  $\delta$  3.87 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.65 (s, 3H, OMe), 3.39 (s, 3H, OMe), 3.14 (d, 1H,  $J = 13.7$  Hz,  $\text{C}_6 \text{H}_{\text{exo}}$ ), 2.17 (d, 1H,  $J = 13.7$  Hz,  $\text{C}_6 \text{H}_{\text{endo}}$ ), 1.70 (Me);  $^{13}\text{C}$  NMR  $\delta$  172.1 (-O-C=O), 166.9 (-O-C=O), 165.7 (-O-C=O), 109.4 ( $\text{C}_7$ ), 84.5 (bridgehead,  $\text{C}_1$ ), 70.3 ( $\text{C}_4$ ), 53.2 (OMe), 53.0 (OMe), 51.63 (OMe), 51.61 (OMe), 49.3 ( $\text{C}_5$ ), 42.1 ( $\text{C}_6$ ), 21.7 (Me); IR (KBr): 2850, 1790, 1720, 1420, 1320, 1260, 1000, 940  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{13}\text{H}_{18}\text{BrO}_8$ : C 40.86, H 4.75; Found: C 40.89, H 4.73.

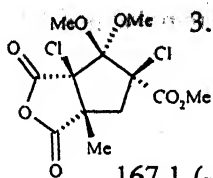
**1,7-Dichloro-3-hydroxy-8,8-dimethoxy-2,5-dioxo-4-oxa-****tricyclo[4.2.1.0<sup>3,7</sup>]nonane-9-carboxylic acid methyl ester 74: Yield:**

40%, colorless solid (EtOAc); mp 152-154 °C;  $^1\text{H}$  NMR ( $\text{CDCl}_3$ :DMSO, 20:1)  $\delta$  3.89 (d, 1H,  $J = 11.0$  Hz), 3.75 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.64 (s, 3H, OMe), 3.62 (d, 1H,  $J = 11.0$  Hz);  $^{13}\text{C}$  NMR  $\delta$  190.7 (-C=O), 168.1 (-O-C=O), 167.1 (-O-C=O), 101.5, 101.0, 76.4, 74.1, 53.6, 53.1, 53.0, 51.8, 50.6; IR (KBr): 3150, 2900, 1760 (br), 1430, 1370  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{12}\text{H}_{12}\text{Cl}_2\text{O}_8$ : C 40.59, H 3.41; Found: C 40.58, H 3.42.



**4-Chloro-7,7-dimethoxy-5-methyl-3-oxo-2-oxa-****bicyclo[2.2.1]heptane-1,5-dicarboxylic acid dimethyl ester 76:**Yield: 57%; colorless solid (dichloromethane/hexane), mp 88-90 °C;  $^1\text{H}$ 


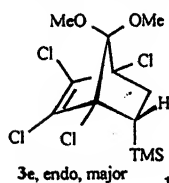
NMR  $\delta$  3.88 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.87 (s, 3H, OMe), 3.10 (d, 1H,  $J = 13.6$  Hz, C(6)H<sub>exo</sub>), 2.67 (d, 1H,  $J = 13.6$  Hz, C(6)H<sub>endo</sub>), 1.67 (Me);  $^{13}\text{C}$  NMR  $\delta$  172.3 (-O-C=O), 167.1 (-O-C=O), 165.7 (-O-C=O), 109.4 (C<sub>7</sub>), 83.9 (bridgehead, C<sub>1</sub>), 77.2 (C<sub>4</sub>), 53.3 (OMe), 53.2 (OMe), 51.8 (OMe), 51.7 (OMe), 49.2 (C<sub>5</sub>), 41.8 (C<sub>6</sub>), 20.3 (Me); IR (KBr) 2900, 1790, 1700, 1430, 1320  $\text{cm}^{-1}$ ; Anal. calcd. for C<sub>13</sub>H<sub>18</sub>ClO<sub>8</sub>: C 46.23, H 5.37; Found: C 46.25, H 5.39.

**3a,5-Dichloro-4,4-dimethoxy-6a-methyl-1,3-dioxo-hexahydro-****cyclopenta[c]furan-5-carboxylic acid methyl ester 77:** Yield: 14%; colorless solid (dichloromethane/hexane), mp 122-124 °C;  $^1\text{H}$  NMR  $\delta$ 


3.85 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.54 (d, 1H,  $J = 15.6$  Hz), 3.31 (s, 3H, OMe), 2.42 (d, 1H,  $J = 15.6$  Hz), 1.69 (Me);  $^{13}\text{C}$  NMR  $\delta$  173.3 (-O-C=O), 167.1 (-O-C=O), 119.7, 72.5, 53.9, 53.7, 51.9, 45.7, 23.4; IR (KBr) 2850, 1850, 1780, 1720, 1420, 1240, 1200  $\text{cm}^{-1}$ .

**Trimethyl-(1,4,5,6-tetrachloro-7,7-dimethoxy-bicyclo[2.2.1]hept-5-en-2-yl)-silane 3e,e<sub>1</sub>:** Yield: 73%; mixture of regioisomers (97:3), obtained as a viscous liquid.

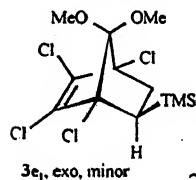
**Major isomer 3e:**  $^1\text{H}$  NMR  $\delta$  3.60 (s, 3H, OMe), 3.51 (s, 3H, OMe),



2.45 (dd, 1H,  $J = 11.2, 9.8$  Hz C(3)H<sub>exo</sub>), 1.95 (dd, 1H,  $J = 9.8, 5.2$  Hz, C(2)H<sub>exo</sub>), 1.70 (dd, 1H,  $J = 11.2, 5.2$  Hz, C(3)H<sub>endo</sub>), 0.04 (s, 9H, SiMe<sub>3</sub>);  $^{13}\text{C}$  NMR  $\delta$  130.5, 129.0, 112.2 (C<sub>7</sub>), 78.5 (bridgehead), 75.2 (bridgehead),

52.9 (OMe), 51.7 (OMe), 37.5, 35.4, -1.9 (3C, Me); IR (KBr) 2900, 1600, 1440, 1240, 1180  $\text{cm}^{-1}$ .

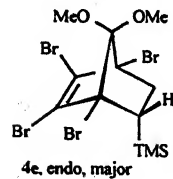
**Minor isomer 3e<sub>1</sub>:** (partial data from the mixture);  $^1\text{H}$  NMR  $\delta$  2.16



(dd, 1H,  $J = 12.6, 7.1$  Hz C(3)H<sub>exo</sub>), 1.27 (dd, 1H,  $J = 10.7, 7.1$  Hz, C(3)H<sub>endo</sub>), 0.09 (s, 9H, SiMe<sub>3</sub>);  $^{13}\text{C}$  NMR  $\delta$  129.6, 128.7, 76.0, 52.9 (OMe), 51.2 (OMe), 39.8, 37.7, -1.6 (3C, Me).

**Trimethyl-(1,4,5,6-tetrabromo-7,7-dimethoxy-bicyclo[2.2.1]hept-5-en-2-yl)-silane 4e,e<sub>1</sub>:** Yield: 52%; mixture of regioisomers (96:4), obtained as a viscous liquid.

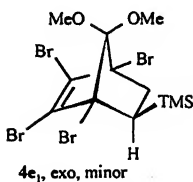
**Major isomer 4e:**  $^1\text{H}$  NMR  $\delta$  3.55 (s, 3H, OMe), 3.50 (s, 3H, OMe),



2.41 (dd, 1H,  $J = 11.3, 9.7$  Hz C(3)H<sub>exo</sub>), 1.93 (dd, 1H,  $J = 9.7, 5.2$  Hz, C(2)H<sub>exo</sub>), 1.66 (dd, 1H,  $J = 11.3, 5.2$  Hz, C(3)H<sub>endo</sub>), 0.06 (s, 9H, SiMe<sub>3</sub>);  $^{13}\text{C}$  NMR  $\delta$  126.7, 124.9, 112.3 (C<sub>7</sub>), 72.3 (bridgehead), 68.8 (bridgehead),

53.3 (OMe), 51.7 (OMe), 39.4, 37.1, -1.5 (3C, Me); IR (KBr) 2900, 1560, 1440, 1240, 1140  $\text{cm}^{-1}$ .

**Minor isomer 4e<sub>1</sub>:** (data from the mixture); <sup>1</sup>H NMR δ 3.53 (s, 3H,

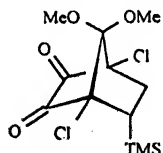


OMe), 3.50 (s, 3H, OMe, merged with OMe of major isomer), 2.16 (dd, 1H,  $J = 11.4, 6.8$  Hz C(3)H<sub>exo</sub>), 1.83 (dd, 1H,  $J = 11.4, 10.1$  Hz, C(3)H<sub>endo</sub>), 1.23 (dd, 1H,  $J = 11.1, 6.8$  Hz, C(3)H<sub>endo</sub>), 0.12 (s, 9H, SiMe<sub>3</sub>); <sup>13</sup>C

NMR δ 129.7, 124.3, 110.0, 77.3 (bridgehead), 69.7 (bridgehead), 53.4 (OMe), 51.2 (OMe), 41.1, 39.4, 31.2, -1.2 (3C, Me).

**Dichloro-dimethoxy-trimethylsilyl-bicyclo[2.2.1]heptane-2,3-**

**dione 1e:** Yield: 82%, yellow solid (hexane); mp 67-69 °C; <sup>1</sup>H NMR δ 3.73 (s, 3H, OMe), 3.55 (s, 3H, OMe), 2.67 (dd, 1H,  $J_1 = J_2 = 13.3$  Hz

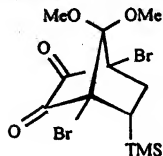


C(5)H<sub>exo</sub>), 2.19 (dd, 1H,  $J = 13.6, 5.9$  Hz, C(6)H<sub>exo</sub>), 1.90 (dd, 1H,  $J = 13.0, 5.9$  Hz, C(6)H<sub>endo</sub>), 0.00 (s, 9H, SiMe<sub>3</sub>); <sup>13</sup>C NMR δ 189.2 (-C=O), 189.1 (-C=O), 102.5

(C<sub>7</sub>), 78.9 (bridgehead), 75.6 (bridgehead), 52.6 (OMe), 51.9 (OMe), 33.3, 30.5, -2.5 (3C, Me); IR (KBr) 2900, 1740, 1420 cm<sup>-1</sup>; Anal. calcd. for C<sub>12</sub>H<sub>18</sub>Cl<sub>2</sub>O<sub>4</sub>Si: C 44.31, H 5.58; Found: C 44.33, H 5.55.

**Dibromo-dimethoxy-trimethylsilyl-bicyclo[2.2.1]heptane-2,3-**

**dione 2e:** Yield: 78%, yellow solid (hexane); mp 68-70 °C; <sup>1</sup>H NMR δ 3.77 (s, 3H, OMe), 3.58 (s, 3H, OMe), 2.73 (dd, 1H,  $J_1 =$



$J_2 = 13.4$  Hz C(5)H<sub>exo</sub>), 2.25 (dd, 1H,  $J = 13.4, 6.0$  Hz, C(6)H<sub>exo</sub>), 1.96 (dd, 1H,  $J = 12.8, 6.0$  Hz, C(6)H<sub>endo</sub>),

0.00 (s, 9H, SiMe<sub>3</sub>); <sup>13</sup>C NMR δ 188.6 (-C=O), 188.3 (-C=O), 102.8



(C<sub>7</sub>), 71.0 (bridgehead), 67.5 (bridgehead), 52.9 (OMe), 51.0 (OMe), 35.6, 32.2, -2.2 (3C, Me); IR (KBr) 2850, 1750, 1420, 1400 cm<sup>-1</sup>; Anal. calcd. for C<sub>12</sub>H<sub>18</sub>Br<sub>2</sub>O<sub>4</sub>Si: C 34.80, H 4.38; Found: C 34.83, H 4.40.

**1,3-Dichloro-2,2-dimethoxy-4-trimethylsilyl-cyclopentane-1,3-dicarboxylic acid dimethyl ester 79:** Yield: 80%; colorless solid, mp

61-63 °C; <sup>1</sup>H NMR δ 3.73 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.16 (s, 3H, OMe), 2.84 (dd, 1H, *J*<sub>1</sub> = *J*<sub>2</sub> = 14.5 Hz, C<sub>5</sub> H<sub>β</sub>), 2.19 (dd, 1H, *J* = 15.0, 5.7 Hz, C<sub>4</sub> H<sub>β</sub>), 1.96 (dd, 1H, *J* = 15.0, 5.7 Hz, C<sub>5</sub> H<sub>α</sub>), 0.03 (9H, SiMe<sub>3</sub>); <sup>13</sup>C NMR δ 169.6 (-O-C=O), 168.5 (-O-C=O), 112.3 (C<sub>2</sub>), 80.0, 76.7, 54.1, 53.3, 52.9, 51.9, 39.2, -1.3 (C<sub>4</sub>); IR (KBr) 2900, 1720 (br), 1430 cm<sup>-1</sup>; Anal. calcd. for C<sub>14</sub>H<sub>24</sub>Cl<sub>2</sub>O<sub>6</sub>Si: C 43.41, H 6.25; Found: C 43.43, H 6.29.

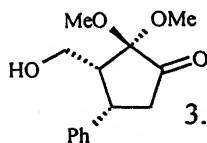
**1,3-Bis-hydroxymethyl-2,2-dimethoxy-4-phenyl-cyclopentanol 81:**

Yield: 89%; colorless solid; mp 83-84 °C; <sup>1</sup>H NMR δ 7.32-7.19 (m, 5H, aromatic), 4.39 (br, s, 1H, OH, D<sub>2</sub>O exchangeable), 3.80 (½ ABq, 1H, *J* = 11.5 Hz), 3.73 (½ ABq, 1H, *J* = 11.5 Hz), 3.54 (m, 2H), 3.45 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.33-3.25 (m, 1H), 3.05 (br, s, 1H, OH, D<sub>2</sub>O exchangeable), 2.52-2.46 (m, 2H), 2.24 (dd, 1H, *J*<sub>1</sub> = *J*<sub>2</sub> = 13.3 Hz); <sup>13</sup>C NMR δ 139.9, 128.3, 128.0, 126.4, 111.5 (C<sub>2</sub>), 81.4 (C<sub>1</sub>), 67.0 (CH<sub>2</sub>), 59.2 (CH<sub>2</sub>), 50.4 (CH), 49.2 (CH<sub>3</sub>), 49.0 (CH<sub>3</sub>), 41.6 (CH<sub>2</sub>), 40.9 (CH); IR (KBr) 3200,

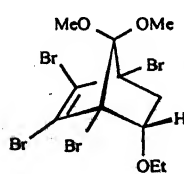
2900, 1600, 1580, 1440  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{15}\text{H}_{22}\text{O}_5$ : C 63.81, H 7.85; Found: C 63.83, H 7.88.

**3-Hydroxymethyl-2,2-dimethoxy-4-phenyl-cyclopentanone 82:**

Yield: 93%; colorless solid; mp 112 °C;  $^1\text{H}$  NMR  $\delta$  7.38-7.14 (m, 5H, aromatic), 3.83 (ddd, 1H,  $J = 10.7, 9.2, 7.1$  Hz, benzylic hydrogen), 3.62 (dd, 1H,  $J = 12.2, 3.1$  Hz), 3.50 (s, 3H, OMe), 3.36 (dd, 1H,  $J = 12.2, 3.4$  Hz), 3.33 (s, 3H, OMe), 2.93 (dd, 1H,  $J = 19.3, 11.5$  Hz), 2.59 (dd, 1H,  $J = 19.3, 9.2$  Hz), 2.54-2.52 (m, 1H), 1.93 (t, 1H,  $J = 5.9$  Hz, OH,  $\text{D}_2\text{O}$  exchangeable);  $^{13}\text{C}$  NMR  $\delta$  208.5 ( $-\text{C}=\text{O}$ ), 139.1, 128.6, 127.9, 126.9, 103.2, 58.7, 51.0, 50.3, 48.9, 39.1, 38.4; IR (KBr) 3500, 2900, 1760, 1600, 1500, 1450, 1400, 1300, 1220  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{14}\text{H}_{18}\text{O}_4$ : C 67.18, H 7.25; Found: C 67.21, H 7.27.



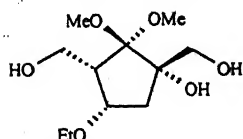
**1,2,3,4-Tetrabromo-5-ethoxy-7,7-dimethoxy-bicyclo[2.2.1]hept-2-ene 2b:** Yield: 86%, colorless solid; mp 58-60 °C;  $^1\text{H}$  NMR  $\delta$  4.32 (dd,



1H,  $J = 7.6, 2.3$  Hz, C(5) $\text{H}_{\text{exo}}$ ), 3.77-3.71 (m, 1H,  $\text{CH}_2$ ), 3.60 (s, 3H, OMe), 3.56-3.52 (m, 1H,  $\text{CH}_2$ ), 2.62 (dd, 1H,  $J = 12.2, 7.6$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 1.76 (dd, 1H,  $J = 12.2, 2.3$  Hz, C(6) $\text{H}_{\text{endo}}$ ), 1.15 (t, 3H,  $J = 7.0$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  126.1, 123.6, 111.6, 85.2, 72.3, 67.8, 66.7, 53.0 (OMe), 52.0 (OMe), 45.5, 15.0 (Me); IR (KBr): 2850, 1560, 1440, 1340  $\text{cm}^{-1}$ .

**4-Ethoxy-1,3-bis-hydroxymethyl-2,2-dimethoxy-cyclopentanol 83:**

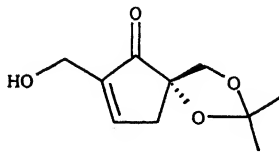
Yield: 85%; colorless viscous liquid;  $^1\text{H}$  NMR  $\delta$  4.30 (br, s, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 3.98 (ddd, 1H,  $J_1 = J_2 = 5.8$ ,  $J_3 = 3.3\text{Hz}$ ), 3.90-3.82 (m, 2H), 3.77 ( $\frac{1}{2}$  ABq, 1H,  $J = 11.6$  Hz), 3.65 ( $\frac{1}{2}$  ABq, 1H,  $J = 11.6$  Hz), 3.66-3.59 (m, 1H), 3.47-3.36 (m, 1H, buried under OMe), 3.40 (s, 3H, OMe), 3.25 (s, 3H, OMe), 2.79 (br, s, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 2.58 (br, s, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 2.45 (q, 1H,  $J = 6.2$  Hz), 2.20 (dd, 1H,  $J = 14.6$ , 5.4 Hz), 1.95 (dd, 1H,  $J = 14.6$ , 3.2 Hz), 1.20 (t, 3H, ,  $J = 7.1$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  110.0 ( $\text{C}_2$ ), 82.9 ( $\text{C}_1$ ), 78.1, 66.3, 65.1, 59.6, 51.5, 50.6, 48.9, 39.9, 15.3 (Me); IR (neat) 3250, 2800, 1700, 1600, 1250, 1020, 940  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{11}\text{H}_{22}\text{O}_6$ : C 52.79, H 8.86; Found: C 52.81, H 8.89.



**Synthesis of 2-hydroxymethyl 4-deoxy pentenomycin derivative:** A solution of triol 83 (200 mg, 0.80 mmol) in anhydrous acetone 5 ml was stirred at room temperature with amberlyst-15 (80-100mg) and few pieces of molecular sieves for 7 h. The resin was filtered off, solvent was removed and the residue was purified by column chromatography using silica gel (50-60% EtOAc-Hexane) to furnish 110.6 mg of 48 (70%).

**2-hydroxymethyl 4-deoxy pentenomycin derivative 48:** Yield: 70%; colorless viscous liquid;  $^1\text{H}$  NMR  $\delta$  7.53-7.50 (m, 1H, C(8) olefinic H), 4.35 (s, 2H), 4.03 ( $\frac{1}{2}$  ABq, 1H,  $J = 8.5$  Hz), 3.95 ( $\frac{1}{2}$  ABq, 1H,  $J = 8.5$

Hz), 2.86-2.84 (m, 2H), 2.54 (br s, 1H, OH, D<sub>2</sub>O exchangeable), 1.53 (s, 3H, Me), 1.47 (s, 3H, Me); <sup>13</sup>C NMR δ 205.2 (-C=O), 156.1 (C<sub>8</sub>), 143.5 (C<sub>7</sub>), 112.0 (C<sub>2</sub>), 83.1 (C<sub>5</sub>), 73.3, 57.5, 41.4, 26.8 (Me), 25.8 (Me); IR (neat) 3300, 2900, 1700, 1610, 1360 cm<sup>-1</sup>; Anal. calcd. for C<sub>10</sub>H<sub>14</sub>O<sub>4</sub>: C 60.59, H 7.12; Found: C 60.63, H 7.14.



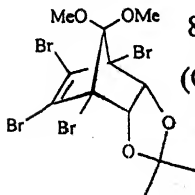
### 3-Chloro-4-ethoxy-1,3-bis-hydroxymethyl-2,2-dimethoxy-

**cyclopentanol 84:** Yield: 71%; colorless viscous liquid; <sup>1</sup>H NMR δ 4.21 (dd, 1H, *J* = 12.7, 7.2 Hz, (in D<sub>2</sub>O exchange, *d*, *J* = 12.7 Hz, *J* = 7.2 Hz is not seen), 4.02 (s, 1H, OH, D<sub>2</sub>O exchangeable), 3.98 (dd, 1H, *J* = 4.6, 2.7 Hz, C(4)H<sub>β</sub>), 3.75-3.48 (m, 3H), 3.49 (s, 3H, OMe), 3.46 (s, 3H, OMe), 2.71 (br s, 1H, OH, D<sub>2</sub>O exchangeable), 2.59 (dd, 1H, *J* = 14.6, 4.6 Hz, C(5)H<sub>β</sub>), 2.54 (br, s, 1H, OH, D<sub>2</sub>O exchangeable, merged with C(5)H<sub>β</sub>), 1.81 (dd, 1H, 2.45, *J* = 14.6, 4.6 Hz, C(5)H<sub>α</sub>), 1.22 (t, 3H, , *J* = 7.1 Hz, Me); <sup>13</sup>C NMR δ 110.2 (C<sub>2</sub>), 84.9, 84.5, 84.1, 66.5, 66.4, 63.7, 52.7, 51.9, 38.0, 15.4 (Me); IR (neat) 3250, 2900, 1440 cm<sup>-1</sup>; Anal. calcd. for C<sub>11</sub>H<sub>21</sub>ClO<sub>6</sub>: C 46.40, H 7.43; Found: C 46.44, H 7.46.

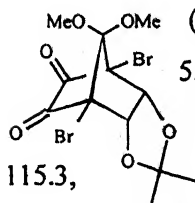
**1,4,5,6-Tetrabromo-7,7-dimethoxy-bicyclo[2.2.1]hept-5-ene-2,3-diol 4o:** Yield: 78%; colorless solid, mp 126-128 °C; <sup>1</sup>H NMR δ 4.92 (s, 2H), 3.62 (s, 3H, OMe), 3.60 (s, 3H, OMe), 1.43 (s, 3H, Me), 1.32 (s,

3H, Me);  $^{13}\text{C}$  NMR  $\delta$  124.3 (2C), 110.4, 77.3 (2C,  $\text{C}_2$ ,  $\text{C}_3$ ), 72.9 (bridgehead), 53.1 (OMe), 51.8 (OMe); IR (KBr) 3300, 2900, 1560, 1440  $\text{cm}^{-1}$ .

**1,7,8,9-Tetrabromo-10,10-dimethoxy-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.0<sup>2,6</sup>]dec-8-ene 4p:** Yield: 87%; colorless solid, mp 126-128  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  4.92 (s, 2H), 3.62 (s, 3H, OMe), 3.60 (s, 3H, OMe), 1.43 (s, 3H, Me), 1.32 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  124.5 (2C), 115.4 (2C), 87.1 (2C), 70.3 (2C, bridgehead), 52.9 (OMe), 52.8 (OMe), 25.5 (2C, Me); IR (KBr) 2900, 1560, 1430, 1380  $\text{cm}^{-1}$ .



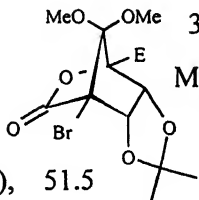
**1,7-Dibromo-10,10-dimethoxy-4,4-dimethyl-3,5-dioxatricyclo[5.2.1.0<sup>2,6</sup>]decane-8,9-dione 2p:** Yield: 95%; yellow solid (dichloro methane/hexane), mp 138-140  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  5.06 (s, 2H), 3.76 (s, 3H, OMe), 3.59 (s, 3H, OMe), 1.31 (s, 6H, Me);  $^{13}\text{C}$  NMR  $\delta$  183.7 ( $-\text{C}=\text{O}$ , 2C), 115.3, 115.3, 105.0, 69.7 (2C, bridgehead), 52.7 (OMe), 52.4 (OMe), 25.3 (Me), 23.9 (Me); IR (KBr) 2900, 1760, 1440, 1370  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{12}\text{H}_{14}\text{Br}_2\text{O}_6$ : C 34.81, H 3.41; Found: C 34.79, H 3.43.



**1-Bromo-10,10-dimethoxy-4,4-dimethyl-9-oxo-3,5,8-trioxatricyclo[5.2.1.0<sup>2,6</sup>]decane-7-carboxylic acid methyl ester 52p:** Yield: 97%; colorless solid, mp 150-152  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  5.34 (d, 1H,  $J = 7.4$

Hz), 4.91 (d, 1H,  $J = 7.4$  Hz), 3.90 (s, 3H, CO<sub>2</sub>Me), 3.64 (s, 3H, OMe),

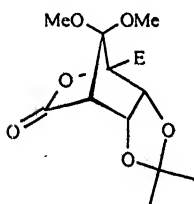
3.41 (s, 3H, OMe), 1.49 (s, 3H, Me), 1.36 (s, 3H, Me); <sup>13</sup>C NMR  $\delta$  164.6 (-O-C=O), 116.3, 111.1 (C<sub>10</sub>), 83.9 (bridgehead, C<sub>7</sub>), 81.7, 81.0, 66.9 (bridgehead, C<sub>1</sub>), 51.5 (OMe), 52.0 (OMe), 25.6 (Me), 25.4 (Me); IR (KBr) 2900, 1780, 1720, 1430, 1360 cm<sup>-1</sup>; Anal. calcd. for C<sub>13</sub>H<sub>17</sub>BrO<sub>8</sub>: C 40.96, H 4.50; Found: C 40.99, H 4.53.



**10,10-Dimethoxy-4,4-dimethyl-9-oxo-3,5,8-trioxa-**

**tricyclo[5.2.1.0<sup>2,6</sup>]decane-7-carboxylic acid methyl ester 55p:** Yield:

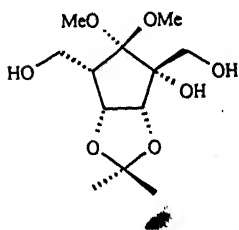
84%; mp 130-132 °C; <sup>1</sup>H NMR  $\delta$  5.30 (d, 1H,  $J = 7.1$  Hz), 4.86 (d, 1H,



$J = 6.8, 4.6$  Hz), 3.89 (s, 3H, CO<sub>2</sub>Me), 3.45 (d, 1H,  $J = 4.4$  Hz), 3.37 (s, 3H, OMe), 3.30 (s, 3H, OMe), 1.49 (s, 3H, Me), 1.35 (s, 3H, Me); <sup>13</sup>C NMR  $\delta$  167.6 (-O-C=O), 165.6, 115.6, 113.3, 85.8 (bridgehead, C<sub>7</sub>), 81.8, 74.5, 55.2 (bridgehead, C<sub>1</sub>),

53.2, 51.8 (OMe), 51.1 (OMe), 25.6 (Me), 25.2 (Me); IR (KBr) 2900, 1800, 1730, 1430, 1370 cm<sup>-1</sup>; Anal. calcd. for C<sub>13</sub>H<sub>18</sub>O<sub>8</sub>: C 51.66, H 6.00; Found: C 51.68, H 6.03.

**4,6-Bis-hydroxymethyl-5,5-dimethoxy-2,2-dimethyl-tetrahydro-cyclopenta-1,3-dioxol-4-ol 88:** Yield: 80 %; colourless viscous liquid;

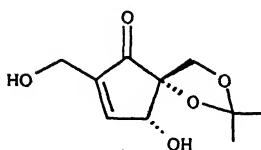


$^1\text{H}$  NMR  $\delta$  4.67 (t, 1H,  $J = 7.1$  Hz), 4.60 (d, 1H,  $J = 7.1$  Hz), 3.96 (d  $\frac{1}{2}$  ABq,  $J = 11.3, 7.7$  Hz), 3.91 (d  $\frac{1}{2}$  ABq,  $J = 11.3, 6.2$  Hz), 3.79 ( $\frac{1}{2}$  ABq, 1H,  $J = 11.7$  Hz), 3.71-3.68 (m, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 3.68 (1/2 ABq, 1H,  $J = 11.7$  Hz, merged with OH,  $J$  was calculated from  $\text{D}_2\text{O}$  spectra), 3.40 (s, 3H, OMe), 3.27 (s, 3H, OMe), 2.55 (ddd, 1H,  $J_1 = J_2 = 10.4$  Hz,  $J_3 = 6.9$  Hz), 1.69 (m, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 1.54 (s, 3H, Me), 1.37 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  112.3, 109.4, 80.1, 79.6, 65.1, 62.8, 59.9, 50.9, 49.0, 48.1, 25.6 (Me), 24.5 (Me); IR (neat) 3200, 2950, 1400  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{12}\text{H}_{22}\text{O}_7$ : C 51.79, H 7.97; Found: C 51.82, H 7.80.

**Synthesis of hydroxymethyl pentenomycin derivatives:** A solution of triol **88** (20 mg, 0.072 mmol) in anhydrous acetone 2 ml was stirred at room temperature with amberlyst-15 (5-7mg) and few pieces of molecular sieves for 7 h. The resin was filtered off, solvent was removed and the residue was purified by column chromatography using silica gel to furnish 72:28 mixture of pentenomycin derivatives **49** and **89** in 49% (7.6 mg) of yield.

**2-hydroxymethyl-pentenomycin derivative 49:** obtained as colorless viscous liquid,  $^1\text{H}$  NMR  $\delta$  7.50-7.49 (m, 2H), 4.55-4.52 (m, 1H), 4.43-4.42 (m, 2H), 4.22 (1/2 ABq,  $J = 8.8$  Hz), 4.07 (1/2 ABq,  $J = 9.0$  Hz),

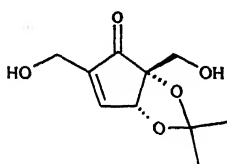
2.85 (d,  $J = 6.6$  Hz, 1H, OH, D<sub>2</sub>O exchangeable), 1.56 (s, 6H, Me); <sup>13</sup>C



NMR  $\delta$  202.2, 156.4, 146.0, 113.0, 82.4, 72.5, 71.0, 57.5, 26.5, 25.4; IR (neat) 3200, 2950, 1700, 1610, 1400  $\text{cm}^{-1}$ ; Anal. calcd. for C<sub>10</sub>H<sub>14</sub>O<sub>5</sub>: C 56.07, H 6.59;

Found: C 56.11, H 6.62.

**2-hydroxymethyl-pentenomycin derivative 89:** colorless viscous liquid; <sup>1</sup>H NMR  $\delta$  7.52 (m, 1H), 5.21 (s, 1H), 4.41 (s, 2H), 3.90-3.86



(m, 2H), 1.47 (s, 3H, Me), 1.34 (s, 3 H, Me). <sup>13</sup>C NMR  $\delta$  204.2, 154.2, 146.3, 115.4, 85.8, 82.4, 77.2, 61.5, 28.8, 28.6. IR (neat) 3200, 2950, 1710, 1600  $\text{cm}^{-1}$ .

**Preparation of Diels-Alder adducts:** The reaction condition of new Diels-Alder adducts reported in Chapter-1A are summarized in the Table-1A.1. The reaction of more reactive i.e., the electron deficient dienophiles were carried out by refluxing diene and a slight excess of dienophile in benzene or under neat condition as specified in Table-1A.1. The remaining were carried out in sealed tubes using benzene as solvent.



## Chapter 1B

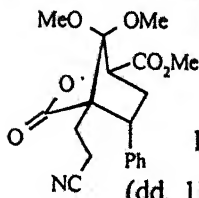
### A Novel Radical Approach to Unusual Spiro-Lactams

**General Procedure for Intermolecular Bridgehead C-C bond Formation:** To a mixture of bromo lactone (1 mmol), alkene (10 mmol) and AIBN (0.025 mmol) in benzene (10 ml) at reflux temperature was added a solution of  $\text{Bu}_3\text{SnH}$  (1.5 mmol) and AIBN (0.025 mmol) in benzene (24 ml) over a period of 45 min. and refluxed for the specified time (Scheme 4). After completion of the reaction, as monitored by tlc benzene was distilled off under reduced pressure and the crude mixture was directly purified on a silica gel column. First 85 ml fractions were collected with hexane as eluent to remove tin impurities and later on polarity of the eluent (ethyl acetate-hexane) was increased to get the pure products.

**Photochemical conditions:** A solution of bromo lactone (0.5 mmol) and alkene (5 mmol) in benzene (5 ml) was irradiated at room temperature with a 200W bulb kept at a distance of 2.5 cm from the reaction flask. A solution of  $\text{Bu}_3\text{SnH}$  (0.75 mmol) in benzene (12 ml) was added over a period of 1h. After the specified time (completion of the starting material as monitored by tlc), benzene was removed under reduced pressure and the crude mixture was directly purified on a silica gel column.

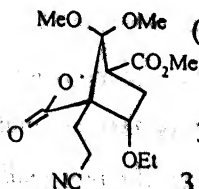
**4-(2-Cyano-ethyl)-7,7-dimethoxy-3-oxo-5-phenyl-2-oxa-**

**bicyclo[2.2.1]heptane-1-carboxylic acid methyl ester 112a:** Yield: 75%; colorless solid (EtOAc/hexane), mp 102-104 °C;  $^1\text{H}$  NMR  $\delta$  7.35-7.28 (m, 3H, aromatic), 7.16-7.11 (m, 2H, aromatic), 3.89 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.63 (s, 3H, OMe), 3.48 (dd, 1H,  $J = 10.5$ , 5.4 Hz, s), 3.36 (s, 3H, OMe), 3.14 (dd, 1H,  $J = 13.9$ , 10.5 Hz), 2.81-2.72 (m, 1H), 2.48-2.40 (m, 1H), 2.24 (dd, 1H,  $J = 13.9$ , 5.4 Hz), 2.13-2.05 (m, 1H), 1.96-1.88 (m, 1H),  $^{13}\text{C}$  NMR  $\delta$  171.1 (O-C=O), 166.7 (O-C=O), 136.6, 128.9, 128.4, 128.3, 119.8 (CN), 112.9, 85.4, 62.7, 53.1 (OMe), 51.6 (OMe), 51.5 (OMe), 45.4, 39.2, 24.3, 12.4; IR (KBr): 2900, 2200, 1770, 1730, 1430  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{19}\text{H}_{21}\text{NO}_6$ : C 63.50, H 5.89, N 3.90; Found: C 63.54, H 5.90, N 3.92.



**4-(2-Cyano-ethyl)-5-ethoxy-7,7-dimethoxy-3-oxo-2-oxa-**

**bicyclo[2.2.1]heptane-1-carboxylic acid methyl ester 112b:** Yield: 72%; colorless solid (EtOAc/hexane), mp 102-104 °C;  $^1\text{H}$  NMR  $\delta$  4.14 (dd, 1H,  $J = 8.0$ , 2.0 Hz), 3.85 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.56-3.49 (m, 1H, merged with OMe, -O-CH<sub>2</sub>), 3.49 (s, 3H, OMe), 3.41 (dq, 1H,  $J = 8.9$ , 7.0 Hz, -O-CH<sub>2</sub>), 3.31 (s, 3H, OMe), 2.94-2.79 (m, 3H), 2.33-3.28 (m, 2H), 1.90 (dd, 1H,  $J = 13.4$ , 2.4 Hz), 1.16 (t, 3H,  $J = 7.0$  Hz, Me),  $^{13}\text{C}$  NMR  $\delta$  170.3 (O-C=O), 166.6 (O-C=O), 120.3 (CN), 111.4, 85.6, 76.7,



65.2, 61.6, 53.1 (OMe), 51.6 (OMe), 51.5 (OMe), 38.7, 23.1, 15.0 (Me), 12.6; IR (KBr): 2900, 1780, 1730, 1430  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{15}\text{H}_{21}\text{NO}_7$ : C 55.04, H 6.47, N 4.28; Found: C 56.01, H 6.49, N 4.30.

**4-(2-Cyano-ethyl)-7,7-dimethoxy-5-methyl-3-oxo-5-phenyl-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid methyl ester 113:** Yield: 33%, colorless solid (dichloromethane/hexane); mp 54-56 °C;  $^1\text{H}$  NMR

$\delta$  7.37-7.26 (m, 5H, aromatic), 3.89 (s, 3H, OMe), 3.60 (s, 3H, OMe), 3.32 (s, 3H, OMe), 2.96 (d, 1H,  $J = 14.1$  Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 2.80 (d, 1H,  $J = 14.3$  Hz,  $\text{C}(6)\text{H}_{\text{endo}}$ ), 2.81-2.72 (m, 1H), 2.66-2.58 (m, 1H), 2.29-2.21 (m, 1H), 2.14-2.06 (m, 1H), 1.79 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  171.2 (-O-C=O), 166.8 (-O-C=O), 141.8, 128.5, 127.7, 127.1, 120.2 (CN), 113.0, 85.3, 65.0, 53.1 (OMe), 51.5 (OMe), 51.1 (OMe), 45.2, 44.9, 22.9, 21.3, 12.6; IR (KBr): 2900, 2200, 1780, 1720, 1600, 1430, 1280, 1260  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{20}\text{H}_{23}\text{NO}_6$ : C 64.33, H 6.21, N 3.75; Found: C 64.35, H 6.23, N 3.73.

**7,7-Dimethoxy-5-methyl-3-oxo-5-phenyl-2-oxa-**

**bicyclo[2.2.1]heptane-1-carboxylic acid methyl ester 114:** Yield:

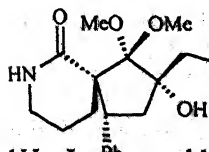
40%, colorless solid (dichloromethane/hexane); mp 104-106 °C;  $^1\text{H}$  NMR  $\delta$  7.33-7.17 (m, 5H, aromatic), 3.86 (s, 3H, OMe), 3.46 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.25 (s, 1H), 2.95 (d, 1H,  $J = 13.7$  Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ),

2.83 (d, 1H,  $J = 13.7$  Hz, C(6)H<sub>endo</sub>), 1.64 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  170.3 (-O-C=O), 167.0 (-O-C=O), 145.5, 128.6, 126.7, 126.1, 111.6, 87.4 (C<sub>1</sub>), 58.3 C<sub>4</sub>), 53.0 OMe), 52.0 (OMe), 51.1 (C<sub>3</sub>), 44.0 (C<sub>6</sub>), 43.9 (C<sub>5</sub>), 31.0 (Me); IR (KBr): 2850, 1790, 1720, 1580, 1420cm<sup>-1</sup>; Anal. calcd. for C<sub>17</sub>H<sub>19</sub>O<sub>6</sub>: C 63.94, H 6.00; Found: C 63.92, H 6.02.

**LiAlH<sub>4</sub> reduction of nitriles 112:** To a suspension of LiAlH<sub>4</sub> (2 mmol) in dry THF (5 ml) cooled in an ice bath, the nitrile 112 (1 mmol) in THF was added under argon. The reaction mixture was stirred for 30 min at room temperature till the starting material was fully consumed, as monitored by tlc. The reaction mixture was quenched with EtOAc. Saturated NH<sub>4</sub>Cl solution was added drop by drop till a white precipitate was obtained. The reaction mixture was filtered and washed thoroughly with EtOAc. Concentration of the combined organic filtrate followed by purification of the crude by silica gel column chromatography afforded the pure spiro lactams 105a,b.

**2-Hydroxy-2-hydroxymethyl-1,1-dimethoxy-4-phenyl-7-aza-spiro[4.5]decan-6-one 105a:** Yield: 63%; colorless crystals (EtOAc);

mp 156-158 °C:  $^1\text{H}$  NMR  $\delta$  7.33-7.22 (m, 5H, aromatic), 6.69 (s, 1H, OH, D<sub>2</sub>O exchangeable), 6.06 (br s, 1H, NH, D<sub>2</sub>O exchangeable), 3.85 (dd, 1H,  $J = 11.2, 5.8$  Hz), 3.69 (dd, 1H,  $J = 11.2, 7.1$  Hz), 3.60 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.15-3.13 (m, 1H), 2.95 (dd, 1H,  $J = 12.9, 9.0$  Hz), 2.85-2.82 (m, 2H), 2.69 (dd, 1H,  $J = 14.2, 9.0$  Hz), 2.47

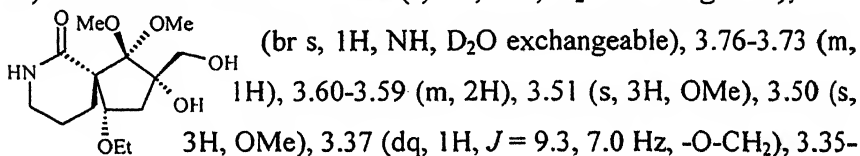


(t, 1H,  $J = 13.5$  Hz), 2.10-2.05 (m, 1H), 1.78-1.67 (m, 1H), 1.29-1.24 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  174.7, 139.9, 129.2, 128.3, 127.1, 113.0, 82.5, 67.7, 62.8, 52.9, 52.3, 52.2, 44.8, 42.5, 28.6, 19.2; IR (KBr): 3200, 2900, 1590, 1440  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{18}\text{H}_{25}\text{NO}_5$ : C 64.46, H 7.51, N 4.18; Found: C 64.43, H 7.50, N 4.19.

**4-Ethoxy-2-hydroxy-2-hydroxymethyl-1,1-dimethoxy-7-aza-**

**spiro[4.5]decan-6-one 105b:** Yield: 61%; colorless solid; mp 98-100

$^{\circ}\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  6.96 (s, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 6.10



3.31 (m, 2H), 2.79 (m, 2H), 2.08-1.98 (m, 3H), 1.93-1.87 (m, 2H), 1.15

(t, 3H,  $J = 7.0$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  173.4, 111.0, 83.8, 81.8, 67.6, 65.1,

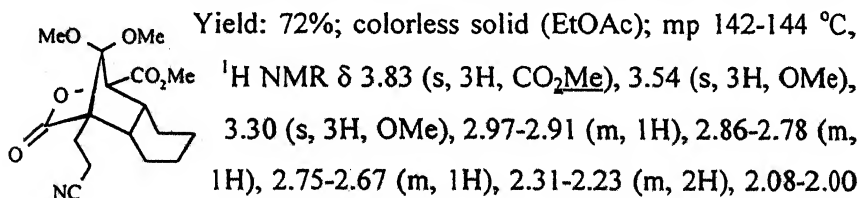
61.6, 52.8, 52.1, 42.9, 42.6, 29.0, 18.9, 15.4; IR (KBr): 3300, 2900,

1610, 1730, 1430  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{14}\text{H}_{25}\text{NO}_6$ : C 55.43, H 8.31, N

4.62; Found: C 55.12, H 8.23, N 4.57.

**1-(2-Cyano-ethyl)-11,11-dimethoxy-10-oxo-9-oxa-**

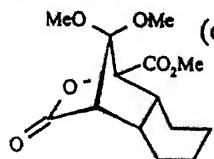
**tricyclo[6.2.1.0<sup>2,7</sup>]undecane-8-carboxylic acid methyl ester 112j:**



(m, 1H), 1.72 (m, 1H), 1.45-1.29 (m, 6H), 1.08-0.98 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  172.3 (O-C=O), 166.7 (O-C=O), 119.8 (CN), 112.2, 88.0, 61.2, 52.8, 51.4, 51.3, 42.0, 38.7, 24.2, 19.2, 18.4, 18.1, 16.1, 12.8; IR (KBr): 2900, 1770, 1720, 1440, 1310  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{17}\text{H}_{23}\text{NO}_6$ : C 60.52, H 6.87, N 4.15; Found: C 60.49, H 6.89, N 4.17.

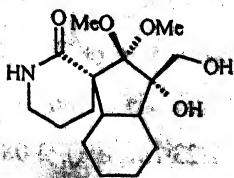
**11,11-Dimethoxy-10-oxo-9-oxa-tricyclo[6.2.1.0<sup>2,7</sup>]undecane-8-**

**carboxylic acid methyl ester 116:** Yield: 23%; colorless solid



(dichloromethane/hexane); mp 120-122  $^{\circ}\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  3.84 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.39 (s, 3H, OMe), 3.29 (s, 3H, OMe), 2.96-2.90 (m, 2H); 2.48-2.40 (m, 1H), 1.75-1.68 (m, 2H), 1.54-1.32 (m, 5H), 1.25-1.16 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  171.5 (O-C=O), 167.0 (O-C=O), 111.1, 89.3, 54.3, 52.8, 51.5, 51.3, 42.6, 32.9, 21.2, 18.8, 18.4, 16.3; IR (KBr): 2900, 1770, 1720, 1440  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_6$ : C 59.14, H 7.09; Found: C 59.17, H 7.11.

**Tricyclic lactam 117:** Yield: 15%; obtained as viscous liquid,  $^1\text{H}$  NMR  $\delta$  7.54 (s, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 6.26 (br s, 1H, NH,  $\text{D}_2\text{O}$  exchangeable), 3.73 (d, 1H,  $J = 11.5$  Hz), 3.64 (d, 1H,  $J = 11.5$



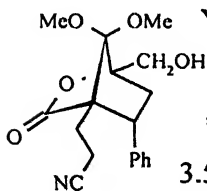
Hz), 3.54 (s, 3H, OMe), 3.47 (s, 3H, OMe), 3.31-3.29 (m, 2H), 2.28 (ddd, 1H,  $J_1 = J_2 = 10.9$  Hz,  $J_3 = 5.8$  Hz), 2.07-2.02 (m, 1H), 1.96-1.81 (m, 3H), 1.81-1.52 (m, 6H), 1.37-1.31 (m,

3H);  $^{13}\text{C}$  NMR  $\delta$  174.9, 112.8, 83.9, 65.7, 61.0, 53.0, 51.4, 48.1, 42.8, 41.8, 31.7, 23.4, 21.1, 19.8, 19.4, 19.1; IR (neat): 3300, 2900, 1600, 1430  $\text{cm}^{-1}$ ; Anal. Calc. for  $\text{C}_{16}\text{H}_{27}\text{NO}_5$ : C 61.32, H 8.68, N 4.47; Found: C 61.35, H 8.70, N 4.50.

**3-(1-Hydroxymethyl-7,7-dimethoxy-3-oxo-5-phenyl-2-oxa-**

**bicyclo[2.2.1]hept-4-yl)-propionitrile 118:** A solution of the nitrile 112a (0.5 mmol) in THF (4 ml) was cooled to 0 °C and  $\text{NaBH}_4$  (0.75 mmol) was added to it. The reaction mixture was stirred for 16 h at rt till the starting material was fully consumed, as monitored by tlc. THF was removed at room temperature under reduced pressure and the residue diluted with water. The aqueous layer was extracted with ethyl acetate (3x5 ml) and the combined organic layer was washed with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Concentration followed by purification of the crude by silica gel column chromatography afforded the pure alcohol.

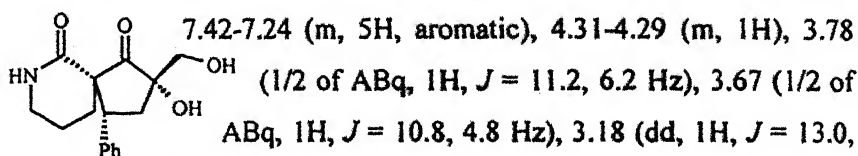
Yield: 84%; colorless solid; mp 130–132 °C,  $^1\text{H}$  NMR  $\delta$  7.27–7.05 (m, 5H, aromatic), 4.08 (1/2 of ABq, 1H,  $J$  = 12.7, 5.5 Hz), 3.93 (1/2 of ABq, 1H,  $J$  = 12.7, 6.4 Hz), 3.51 (s, 3H, OMe), 3.35 (s, 3H, OMe), 3.29 (dd, 1H,  $J$  = 10.5, 5.4 Hz, benzylic H), 2.75–2.67 (m, 1H), 2.61 (dd, 1H,  $J$  = 13.9, 10.5 Hz), 2.42–2.33 (m, 1H), 2.24 (br s, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 2.10 (dd, 1H,  $J$  = 14.2, 5.4 Hz), 2.03–1.95 (m, 1H), 1.86 (dd, 1H,  $J$  = 10.7, 5.7 Hz);  $^{13}\text{C}$  NMR  $\delta$  173.0 (O–C=O), 137.4, 128.7, 128.4,



128.0, 120.1 (CN), 111.5, 90.5, 61.7, 59.8 (CH<sub>2</sub>), 51.9 (CH<sub>3</sub>), 51.4 (CH<sub>3</sub>), 44.5 (CH), 36.7 (CH<sub>2</sub>), 24.4 (CH<sub>2</sub>), 12.4 (CH<sub>2</sub>); IR (KBr): 3300, 2900, 1760, 1440 cm<sup>-1</sup>; Anal. calcd. for C<sub>18</sub>H<sub>21</sub>NO<sub>5</sub>: C 65.24, H 6.39, N 4.23; Found: C 65.17, H 6.35, N 4.25.

**2-Hydroxy-2-hydroxymethyl-4-phenyl-7-aza-spiro[4.5]decane-1,6-dione 119:**

Yield: 93%; colorless solid; mp 120-121 °C, <sup>1</sup>H NMR δ



IR (KBr): 2900, 1750, 1620, 1300 cm<sup>-1</sup>; Anal. calcd. for C<sub>16</sub>H<sub>19</sub>NO<sub>4</sub>: C 66.42, H 6.62, N 4.84; Found: C 66.38, H 6.52, N 4.54.

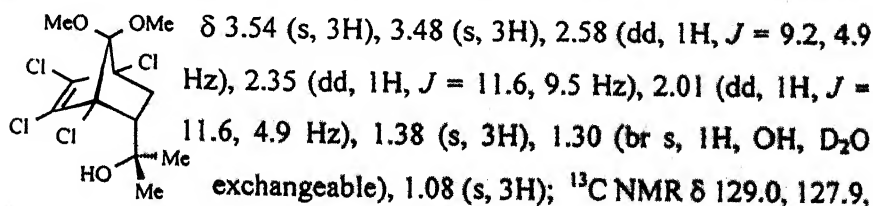


## Chapter 1C

A Short Synthetic Route to  $\gamma$ - and  $\delta$ -Cyclopentannulated Lactones

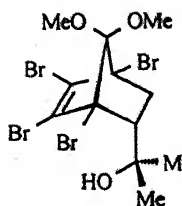
**General procedure for the Grignard reaction of tetrahaloesters 3,4f; Preparation of 123a,b:** An ether solution of methylmagnesium iodide was prepared from Mg turnings (412mg, 17.16 mmol), a crystal of  $I_2$  and MeI (1.6 ml, 25.74 mmol) in 15 ml of dry ether as per standard procedures. After the metal completely dissolved the *endo*-ester derivative 3f (1.0gm, 2.86 mmol) in 5ml of ether was added slowly over 10 minutes under an argon atmosphere. The reaction mixture was stirred for 3.5 h at room temperature (completion of starting material as per tlc), cooled and quenched with saturated  $NH_4Cl$  solution (2 ml). The reaction mixture was extracted thrice with ethyl acetate. The combined organic layer was washed once with brine and dried over anhydrous  $Na_2SO_4$ . The solvent was evaporated and the crude reaction mixture was purified by chromatography using silica gel to yield the tertiary alcohol derivative 123a. Similar reaction conditions were followed for 123b.

**2-(1,4,5,6-Tetrachloro-7,7-dimethoxy-bicyclo[2.2.1]hept-5-en-2-yl)-propan-2-ol 123a:** Yield: 89%, colorless solid, mp 70-71 °C,  $^1H$  NMR

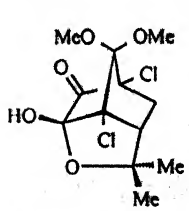


112.5, 77.9, 74.1, 71.3, 54.8, 52.8, 51.6, 38.2, 30.4, 29.5; IR (KBr) 3400, 2900, 1590, 1420, 1240  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{12}\text{H}_{16}\text{Cl}_4\text{O}_3$ : C, 41.17; H, 4.61; Found: C, 41.23; H, 4.64.

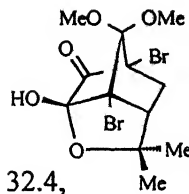
**2-(1,4,5,6-Tetrabromo-7,7-dimethoxy-bicyclo[2.2.1]hept-5-en-2-yl)-propan-2-ol 123b:** Yield: 76%, colorless solid, mp 72-74  $^{\circ}\text{C}$ ,  $^1\text{H}$  NMR

  $\delta$  3.63 (s, 3H), 3.60 (s, 3H), 2.68 (dd, 1H,  $J = 9.2, 4.8$  Hz), 2.47 (dd, 1H,  $J = 11.2, 9.3$  Hz), 2.17 (dd, 1H,  $J = 11.4, 4.9$  Hz), 1.52 (s, 3H), 1.15 (s, 3H);  $^{13}\text{C}$  NMR  $\delta$  125.1, 124.3, 112.7, 71.9, 71.7, 67.8, 56.0, 53.3, 51.7, 40.2, 30.4, 30.1; IR (KBr) 3300, 2900, 1560, 1450,  $\text{cm}^{-1}$ . Anal. Calcd. for  $\text{C}_{12}\text{H}_{16}\text{Br}_4\text{O}_3$ : C, 27.30; H, 3.05; Found: C, 27.23; H, 3.09.

**1,7-Dichloro-3-hydroxy-8,8-dimethoxy-5,5-dimethyl-4-oxatricyclo[4.2.1.0<sup>3,7</sup>]nonan-2-one 124a:** Yield: 84%, colourless solid, mp

 122-124  $^{\circ}\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  3.66 (s, 3H), 3.61 (s, 3H), 2.82 (d, 1H,  $J = 11.0$  Hz), 2.52 (t, 1H,  $J = 12$  Hz), 2.18 (d, 1H,  $J = 13.1$  Hz);  $^{13}\text{C}$   $\delta$  198.8, 102.5, 102.2, 81.9, 76.6, 74.2, 52.6, 52.5, 51.4, 31.2, 29.9, 26.9; IR (KBr) 3250, 2900, 1770, 1420, 1360  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{12}\text{H}_{16}\text{Cl}_2\text{O}_5$ : C, 46.32; H, 5.18; Found: C, 46.44; H 5.21.

**1,7-Dibromo-3-hydroxy-8,8-dimethoxy-5,5-dimethyl-4-oxatricyclo[4.2.1.0<sup>3,7</sup>]nonan-2-one 124b:** Yield: 82%, colourless solid, mp

108-110 °C,  $^1\text{H}$  NMR  $\delta$  3.70 (s, 3H), 3.65 (s, 3H, OMe), 2.9 (d, 1H,  $J =$   
 10.0 Hz), 2.57 (dd, 1H,  $J = 13.0, 11.0$  Hz), 2.24 (d, 1H,  $J = 12.9$  Hz), 1.67 (s, 3H), 1.21 (s, 3H);  $^{13}\text{C}$  NMR  $\delta$   
 198.9, 120.4, 102.2, 81.4, 68.8, 67.1, 54.2, 52.8, 51.5, 32.4, 30.4, 27.4; IR (KBr) 3300, 2900, 1770, 1420  $\text{cm}^{-1}$ ;  
 Anal. Calcd. for  $\text{C}_{12}\text{H}_{16}\text{Br}_2\text{O}_5$ : C, 36.03; H, 4.03; Found: C, 36.14; H 4.07.

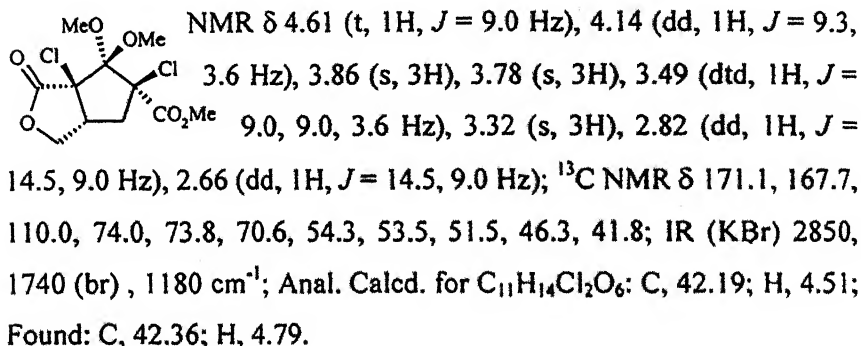
### General procedure for the cleavage of $\alpha$ -keto hemiacetals:

**Method A:** To a stirred solution of the  $\alpha$ -keto hemiacetal (0.17 mmol) in MeOH (1 ml) and benzene (2 ml) was added  $\text{Pb}(\text{OAc})_4$  (102 mg, 0.23 mmol) in portions over a period of 30 min. at room temperature. After stirring for the required time, dil  $\text{NaHCO}_3$  (2 ml) was added and extracted with ethyl acetate. Combined organic layer was washed once with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Concentration followed by silica gel chromatography of the crude yielded the pure  $\gamma$ -lactone-fused cyclopentanes.

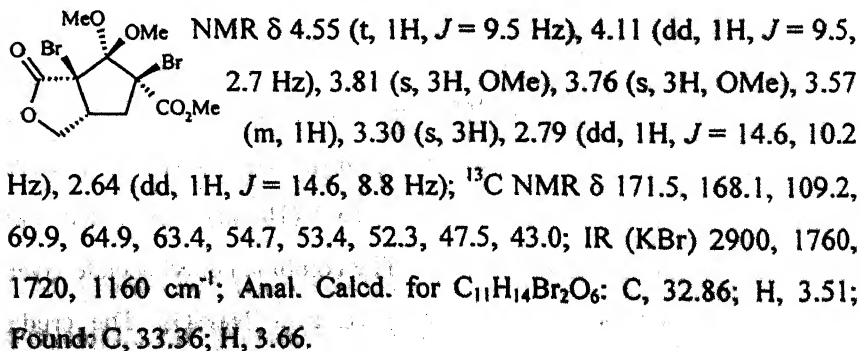
**Method B:** To a stirred solution of  $\alpha$ -keto hemiacetal (0.35 mmol) in methanol (3 ml) was added 30%  $\text{H}_2\text{O}_2$  (0.25 ml) followed by slow addition of 6N  $\text{NaOH}$  solution (0.13 ml). After stirring at room temperature ( $\sim 20^\circ\text{C}$ ) for 1-2 h, 5%  $\text{HCl}$  (10 ml) was added and extracted with ethyl acetate (3 $\times$ 5 ml). The combined ethyl acetate layer was washed once with brine and dried over  $\text{Na}_2\text{SO}_4$ . The crude carboxylic acid obtained after concentration of ethyl acetate layer was

treated with excess diazomethane in ether:methanol (1:1) at 0 °C. After quenching excess diazomethane with acetic acid, the solution was concentrated and silica gel column chromatography afforded the pure product in the specified yields.

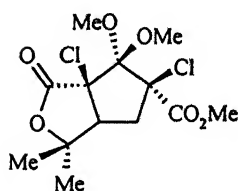
**Methyl 5,6a-Dichloro-6,6-dimethoxy-1-oxo-hexahydro-cyclopenta-[c]furan-5-carboxylate 122a:** Colorless solid; mp 118-120 °C;  $^1\text{H}$



**Methyl 5,6a-Dibromo-6,6-dimethoxy-1-oxo-hexahydro-cyclopenta-[c]furan-5-carboxylate 122b:** Colorless solid; mp 112-113 °C;  $^1\text{H}$



**Methyl 3a,5-Dichloro-4,4-dimethoxy-1,1-dimethyl-3-oxo-hexahydro-cyclopenta[c]furan-5-carboxylate 125a:** Yield 86%;



colorless solid, mp 118-120 °C; <sup>1</sup>H NMR

δ 3.79 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.14 (dd,

1H, *J* = 11.6, 8.5 Hz), 2.81 (dd, 1H, *J* = 14.0, 11.6

Hz), 2.23 (dd, 1H, *J* = 14.0, 8.5 Hz), 1.61 (s, 3H),

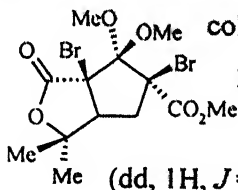
1.24 (s, 3H); <sup>13</sup>C NMR δ 169.9, 167.8, 109.8, 82.9, 75.6, 73.8, 55.6,

54.3, 53.5, 51.5, 36.6, 30.9, 23.7; IR (KBr) 2900, 1730 (br), 1160 cm<sup>-1</sup>;

Anal. Calcd. for C<sub>13</sub>H<sub>18</sub>Cl<sub>2</sub>O<sub>6</sub>: C, 45.76; H, 5.32; Found: C, 45.80; H,

5.46.

**Methyl 3a,5-Dibromo-4,4-dimethoxy-1,1-dimethyl-3-oxo-hexahydro-cyclopenta[c]furan-5-carboxylate 125b:** Yield 81%;



colorless solid, mp 106-109 °C; <sup>1</sup>H NMR δ 3.85 (s,

3H), 3.80 (s, 3H), 3.38 (dd, 1H, *J* = 10.0, 8.5 Hz),

3.31 (s, 3H), 2.90 (dd, 1H, *J* = 14.8, 11.5 Hz), 2.34

(dd, 1H, *J* = 14.4, 8.4 Hz), 1.67 (s, 3H), 1.43 (s, 3H); <sup>13</sup>C NMR

δ 170.4, 168.3, 109.1, 82.9, 65.6, 64.9, 56.4, 54.7, 53.4, 52.1, 38.1,

30.4, 24.1; IR (KBr) 2850, 1760, 1720, 1420 cm<sup>-1</sup>; Anal. Calcd. for

C<sub>13</sub>H<sub>18</sub>Br<sub>2</sub>O<sub>6</sub>: C, 36.30; H, 4.22; Found: C, 36.43; H, 4.31.

**1,2,3,4-Tetrabromo-5-bromomethyl-7,7-dimethoxy-**

**bicyclo[2.2.1]hept-2-ene 4g:** Yield 95%; colorless solid, mp 72-74 °C,

$^1\text{H}$ NMR  $\delta$  3.69-3.61 (m, 1H, merged with OMe), 3.63 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.16-3.11 (m, 1H), 2.83 (dd, 1H,  $J_1 = J_2 = 11.0$  Hz,  $\text{C}_6 \text{H}_{\text{exo}}$ ), 2.59 (dd, 1H,  $J = 12.2, 8.7$  Hz), 1.73 (dd, 1H,  $J = 12.2, 3.9$  Hz);  $^{13}\text{C}$  NMR  $\delta$  127.5, 123.1, 112.0, 72.1, 67.7, 53.0, 51.7 (OMe), 51.5 (OMe), 43.2, 32.7; IR (KBr) 2900, 1580, 1300, 1160  $\text{cm}^{-1}$ .

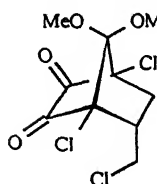
**5-Bromomethyl-1,4-dichloro-7,7-dimethoxy-bicyclo[2.2.1]heptane-**

**2,3-dione 1g:** Yield: 89%; yellow solid; mp 82-84  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  3.74 (s, 3H, OMe), 3.56 (s, 3H, OMe), 3.57-3.53 (m, 1H), 3.21-3.13 (m, 1H), 3.02 (t, 1H,  $J = 10.4$  Hz), 2.83 (dd, 1H,  $J = 13.7, 11.8$  Hz), 2.15 (dd, 1H,  $J = 13.7, 5.1$  Hz);  $^{13}\text{C}$  NMR  $\delta$  187.7, 187.4, 102.5, 79.6, 74.7, 52.8, 52.2, 44.4, 36.9, 30.0; IR (KBr) 2950, 1740, 1420, 1270, 1170  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{10}\text{H}_{11}\text{BrCl}_2\text{O}_2$ : C, 38.25; H, 3.53; Found C, 38.34; H, 3.61.

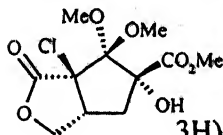
**1,4-Dibromo-5-bromomethyl-7,7-dimethoxy-bicyclo[2.2.1]heptane-**

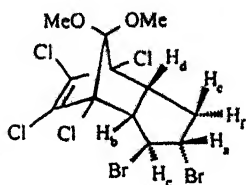
**2,3-dione 2g:** Yield: 80%; yellow solid; mp 69-71  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  3.78 (s, 3H, OMe), 3.60 (s, 3H, OMe), 3.65-3.57 (m, 1H), 3.22-3.16 (m, 1H), 3.00 (t, 1H,  $J = 10.5$  Hz), 2.87 (dd, 1H,  $J = 13.8, 11.8$  Hz), 2.21 (dd, 1H,  $J = 13.8, 5.1$  Hz);  $^{13}\text{C}$  NMR  $\delta$  187.0, 186.8, 102.8, 72.4, 66.3, 52.9, 52.2, 44.8, 38.6, 30.6; IR (KBr) 2950, 1760, 1440  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{10}\text{H}_{11}\text{Br}_3\text{O}_2$ : C, 29.81; H, 2.75; Found C, 29.91; H, 3.01.

**1,4-Dichloro-5-chloromethyl-7,7-dimethoxy-bicyclo[2.2.1]heptane-2,3-dione 1h:** Yield: 90%; yellow solid; mp 76-78 °C;  $^1\text{H}$  NMR  $\delta$  3.75 (s, 3H, OMe), 3.69 (dd, 1H,  $J = 12.1, 3.8$  Hz), 3.56 (s, 3H, OMe), 3.47 (dd, 1H,  $J = 12.0, 6.8$ ), 3.21-3.12 (m, 1H), 2.81 (t, 1H,  $J = 10.4$  Hz), 2.83 (dd, 1H,  $J = 13.6, 12.1$  Hz), 2.30 (dd, 1H,  $J = 13.7, 5.1$ Hz);  $^{13}\text{C}$  NMR  $\delta$  187.8, 187.5, 102.3, 79.0, 74.7, 52.7, 52.0, 44.7, 42.0, 34.9; IR (KBr) 2950, 1750, 1430, 1300, 970  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{10}\text{H}_{11}\text{Cl}_3\text{O}_2$ : C, 44.56; H, 4.11; Found C, 44.60; H, 4.14.9.

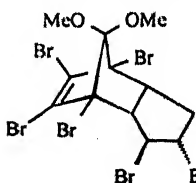


**Methyl 6a-Chloro-5-hydroxy-6,6-dimethoxy-1-oxo-hexahydro-cyclopenta[c]furan-5-carboxylate 126:** Yield: 91%; colorless solid; mp 72-74 °C;  $^1\text{H}$  NMR  $\delta$  4.59 (t, 1H,  $J = 8.8$  Hz), 4.16 (dd, 1H,  $J = 9.0, 2.0$  Hz), 3.81 (s, 3H), 3.75 (s, 3H), 3.50 (br s, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 3.39 (s, 3H), 3.15-3.12 (m, 1H), 3.04 (t, 1H,  $J = 12.5$  Hz), 1.80 (dd, 1H,  $J = 13.9, 2.7$  Hz);  $^{13}\text{C}$  NMR  $\delta$  171.5, 171.3, 107.7, 82.8, 72.1, 71.0, 54.0, 53.1, 50.9, 45.3, 37.5; IR (KBr) 3350, 2900, 1730, 1150  $\text{cm}^{-1}$ . Anal. Calcd. for  $\text{C}_{11}\text{H}_{15}\text{ClO}_7$ : C, 44.83; H, 5.13; Found: C, 44.79; H, 5.08.



**1,2-Dibromo-4,5,6,7-tetrachloro-8,8-dimethoxy-2,3,3a,4,7,7a-****hexahydro-1-H-4,7-methano-indene 131a:** Yield: 91%; colorlesssolid; mp 60-62 °C;  $^1\text{H}$  NMR  $\delta$  3.97 (ddd, 1H,  $J_1$  $= J_2 = 10.7$  Hz,  $J_3 = 6.9$  Hz,  $\text{H}_a$ ), 3.63-3.58 (m,1H,  $\text{H}_b$ ), 3.60 (s, 3H, OMe), 3.55 (s, 3H, OMe),3.30 (dd, 1H,  $J = 9.8, 9.2$  Hz,  $\text{H}_c$ ), 3.16 (ddd, 1H, $J_1 = J_2 = 9.8$  Hz,  $J_3 = 8.5$  Hz,  $\text{H}_d$ ), 2.49 (m, 1H,  $\text{H}_e$ ), 1.51 (ddd,  $J = 12.7,$ 10.7, 10.0 Hz,  $\text{H}_f$ );  $^{13}\text{C}$  NMR  $\delta$  130.4, 129.6, 114.8 ( $\text{C}_8$ ), 76.9, 76.3,

59.6, 52.6m 52.5, 51.8, 51.5, 51.3; IR (KBr) 2900, 1600, 1440, 1300,

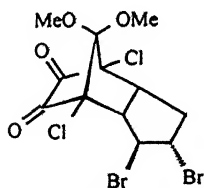
1180  $\text{cm}^{-1}$ .**1,2,4,5,6,7-Hexabromo-8,8-dimethoxy-2,3,3a,4,7,7a-hexahydro-1-H-****4,7-methano-indene 131b:** Yield: 92%; colorless solid; mp 126-127°C;  $^1\text{H}$  NMR  $\delta$  3.97 (ddd, 1H,  $J_1 = J_2 = 10.5$  Hz,  $J_3 = 6.9$  Hz,  $\text{H}_a$ ), 3.66(dd, 1H,  $J = 9.9, 8.7$  Hz,  $\text{H}_b$ ), 3.62 (s, 3H, OMe),3.59 (s, 3H, OMe), 3.34 (dd, 1H,  $J = 8.7, 10.5$ Hz,  $\text{H}_c$ ), 3.25 (ddd, 1H,  $J_1 = J_2 = 9.9$  Hz,  $J_3 = 7.0$ Hz,  $\text{H}_d$ ), 2.49 (ddd, 1H,  $J = 10.0, 6.9$  Hz,  $\text{H}_e$ ),1.51 (m, 1H,  $\text{H}_f$ );  $^{13}\text{C}$  NMR  $\delta$  126.4, 125.7, 114.7 ( $\text{C}_8$ ), 70.0, 60.7,

53.09, 53.06, 52.3, 51.9, 51.7, 34.8; IR (KBr) 2900, 1580, 1460, 1300,

1180  $\text{cm}^{-1}$ .**1,2-Dibromo-4,7-dichloro-8,8-dimethoxy-hexahydro-4,7-methano-****indene-5,6-dione 132a:** Yield: 96%; yellow crystals



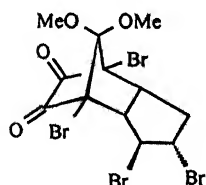
(dichloromethane); mp 138-140 °C;  $^1\text{H}$  NMR  $\delta$  4.07-4.00 (m, 1H,  $\text{H}_a$ ), 3.76 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.50-3.41 (m, 2H), 3.38-3.29 (m,



1H), 2.59 (ddd, 1H,  $J_1 = J_2 = 8.1$  Hz,  $J_3 = 6.8$  Hz), 1.44-1.35 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  187.5 (-C=O), 187.3 (-C=O), 105.0 ( $\text{C}_8$ ), 77.3 (2c), 54.4, 52.8,

52.3, 51.3, 50.3, 46.0, 35.1; IR (KBr) 2900, 1760, 1440, 1300, 1180  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{12}\text{H}_{12}\text{Br}_2\text{Cl}_2\text{O}_4$ : C, 31.96; H, 2.68; Found C, 31.93; H, 2.65.

**1,2,4,7-Tetrabromo-8,8-dimethoxy-hexahydro-4,7-methano-indene-5,6-dione 132b:** Yield: 94%; yellow crystals (dichloromethane); mp 154-156 °C;  $^1\text{H}$  NMR  $\delta$  4.00 (ddd, 1H,  $J = 12.0, 9.5, 6.8$  Hz,  $\text{H}_a$ ), 3.79



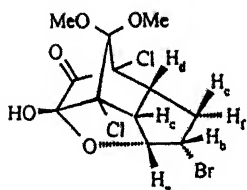
(s, 3H, OMe), 3.62 (s, 3H, OMe), 3.48-3.32 (m, 3H), 2.59 (ddd, 1H,  $J_1 = J_2 = 8.1$  Hz,  $J_3 = 6.8$  Hz),

1.40-1.31 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  186.9 (-C=O), 186.8 (-C=O), 105.3 ( $\text{C}_8$ ), 69.5, 68.4, 55.6, 53.0, 52.4,

51.1, 50.7, 47.7, 35.4; IR (KBr) 2900, 1760, 1430, 1360, 1180  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{12}\text{H}_{12}\text{Br}_4\text{O}_4$ : C, 26.70; H, 2.24; Found C, 26.74; H, 2.27.

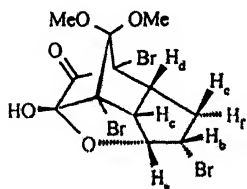
**Hemiacetal 133a:** Yield: 91%; colorless solid; mp 156-158 °C,  $^1\text{H}$  NMR  $\delta$  4.85 (dd, 1H,  $J_1 = J_2 = 3.2$  Hz,  $\text{H}_a$ ), 3.95 (ddd, 1H,  $J = 10.7, 9.0, 2.8$  Hz,  $\text{H}_b$ ), 3.66 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.33 (dd, 1H,  $J = 10.7, 3.7$  Hz,  $\text{H}_c$ ), 3.12 (ddd,  $J_1 = J_2 = 9.6$  Hz,  $J_3 = 6.3$  Hz,  $\text{H}_d$ ), 2.58

(ddd, 1H,  $J_1 = 14.6$  Hz,  $J_2 = J_3 = 9.6$  Hz,  $H_e$ ), 1.64 (ddd,  $J_1 = 14.6$  Hz, 11.2, 6.3 Hz,  $H_f$ );  $^{13}\text{C}$  NMR  $\delta$  194.7 ( $-\text{C}=\text{O}$ ), 104.2, 103.8, 82.8, 78.9,



75.7, 55.4, 52.4, 51.8, 47.3, 43.9, 33.6; IR (KBr) 3400, 2900, 1760, 1430, 1350, 1180  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{12}\text{H}_{13}\text{BrCl}_2\text{O}_5$ : C, 37.14; H, 3.38; Found: C, 37.11; H, 3.40.

**Hemiacetal 133b:** Yield: 88%; colorless solid; mp 168-170  $^\circ\text{C}$ ,  $^1\text{H}$

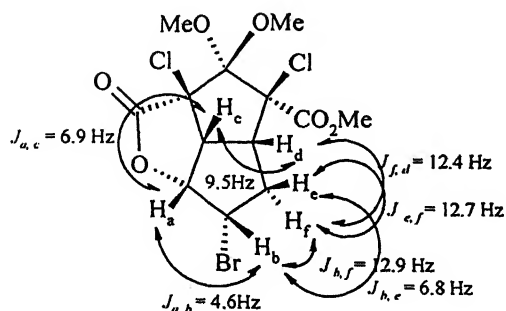


NMR  $\delta$  4.87 (dd, 1H,  $J_1 = J_2 = 3.2$  Hz,  $H_a$ ), 4.03 (br s, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 3.95 (ddd, 1H,  $J_1 = J_2 = 8.7$  Hz 2.7 Hz,  $H_b$ ), 3.69 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.36 (dd, 1H,  $J = 10.8, 3.7$  Hz,  $H_c$ ), 3.12 (ddd,  $J_1 = J_2 = 9.6$  Hz,  $J_3 = 6.4$  Hz,  $H_d$ ), 2.62 (ddd, 1H,  $J_1 = 14.6$  Hz,  $J_2 = J_3 = 9.6$  Hz,  $H_e$ ), 1.64 (1H, ddd, 1H,  $J_1 = 14.6, 11.2, 6.1$  Hz,  $H_f$ );  $^{13}\text{C}$  NMR  $\delta$  194.3 ( $-\text{C}=\text{O}$ ), 104.6, 103.7, 82.6, 71.8, 67.4, 57.2, 52.7, 51.9, 46.9, 45.2, 34.2; IR (KBr) 3300, 2900, 1780, 1440, 1200  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{12}\text{H}_{13}\text{Br}_3\text{O}_5$ : C, 30.22; H, 2.75; Found: C, 30.25; H, 2.73.

**6-Bromo-2a,4-dichloro-3,3-dimethoxy-2-oxo-octahydro-**

**pentaleno[1,6-bc]furan-4-carboxylic acid methyl ester 134:** Yield: 71%; colorless crystals ( $\text{EtOAc}$ ); mp 188-190  $^\circ\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  4.88 (dd, 1H,  $J = 6.9, 4.6$  Hz,  $H_a$ ), 3.95 (ddd, 1H,  $J = 12.9, 6.9, 4.6$  Hz,  $H_b$ ), 3.81 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.73 (dd, 1H,  $J = 9.5, 6.9$  Hz,  $H_c$ ), 3.68 (s, 3H, OMe),

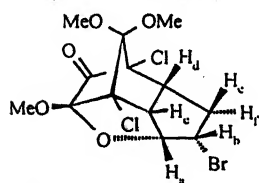
3.35 (s, 3H, OMe), 3.12-3.04 (m, 1H,  $H_d$ ), 2.79-2.72 (m, 1H,  $H_e$ ), 2.47 (ddd,  $J = 12.9, 12.7, 12.4$  Hz,  $H_f$ );  $^{13}\text{C}$  NMR  $\delta$  170.0 (-O-C=O), 166.8 (-



O-C=O), 111.1 ( $\text{C}_3$ ), 80.3, 75.1, 74.8, 56.2, 53.5, 53.4, 52.3, 52.0, 45.2, 36.6; IR (KBr) 2900, 1760, 1720, 1430, 1280, 1170, 1000  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{12}\text{H}_{15}\text{BrCl}_2\text{O}_6$ : C, 35.50;

H, 3.72; Found: C, 35.53; H, 3.74. The assignments of protons  $H_a$ - $H_f$  are confirmed by decoupling experiments. Irradiation of  $H_a$ ,  $H_b$  and  $H_c$  resulted in the disappearance of corresponding couplings. The coupling constants are shown.

**Oxa-tetracyclo acetal 136a:** Yield: 91%; colorless solid; mp 135-137

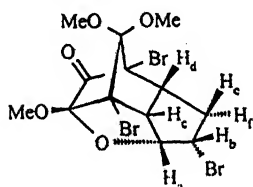


$^{\circ}\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  4.85 (dd, 1H,  $J_1 = J_2 = 3.2$  Hz,  $H_a$ ), 3.95 (ddd, 1H,  $J_1 = J_2 = 9.8, 2.8$  Hz,  $H_b$ ), 3.91 (s, 3H, OMe), 3.64 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.24 (dd, 1H,  $J = 10.7, 3.8$  Hz,  $H_c$ ),

3.04 (ddd,  $J_1 = J_2 = 10.7$  Hz,  $J_3 = 6.1$  Hz,  $H_d$ ), 2.58 (ddd, 1H,  $J_1 = 14.6$  Hz,  $J_2 = J_3 = 9.0$  Hz,  $H_e$ ), 1.65 (ddd,  $J_1 = 14.6$  Hz, 11.2, 6.1 Hz,  $H_f$ );  $^{13}\text{C}$  NMR  $\delta$  194.7 (-C=O), 105.7, 104.1, 83.6, 78.9, 76.6, 55.9, 55.5, 52.4, 51.7, 47.6, 44.0, 33.5; IR (KBr) 2900, 1760, 1430, 1260, 1180  $\text{cm}^{-1}$ ;

Anal. Calcd. for  $C_{13}H_{15}BrCl_2O_5$ : C, 38.83; H, 3.76; Found: C, 38.78; H, 3.79.

**Oxa-tetracyclo acetal 136b:** Yield: 89%; mp 181-183 °C; colorless solid;  $^1H$  NMR  $\delta$  4.86 (dd, 1H,  $J = 3.8, 2.8$  Hz,  $H_a$ ), 4.08 (ddd, 1H,  $J_1 = J_2 = 9.9$  Hz,  $J_3 = 2.7$  Hz,  $H_b$ ), 3.91 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.30 (dd, 1H,  $J = 10.9, 3.8$  Hz,  $H_c$ ), 3.10 (ddd,  $J_1 =$

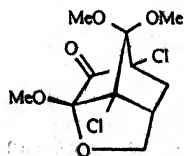


$J_2 = 10.7$  Hz,  $J_3 = 6.1$  Hz,  $H_d$ ), 2.57 (ddd, 1H,  $J_1 = 14.6$  Hz,  $J_2 = J_3 = 9.0$  Hz,  $H_e$ ), 1.60 (1H, ddd, 1H,  $J_1 = 14.6, 11.2, 6.1$  Hz,  $H_f$ );  $^{13}C$  NMR  $\delta$  194.3 (C=O), 104.5, 104.4, 83.4, 72.5, 68.2,

57.5, 55.8, 52.7, 51.8, 47.2, 45.1, 33.9; IR (KBr) 2900, 1760, 1440, 1380, 1200  $cm^{-1}$ ; Anal. Calcd. for  $C_{13}H_{15}Br_3O_5$ : C, 31.80; H, 3.08; Found: C, 31.84; H, 3.06.

**Hemiacetal 120a:** The spectral data for 120a matches with that previously reported from our lab.

**1,7-Dichloro-3,8,8-trimethoxy-4-oxa-tricyclo[4.2.1.0<sup>3,6</sup>]nonan-2-one 139:** Yield: 94%; colorless solid; mp 76-78 °C;  $^1H$  NMR  $\delta$  4.44 (dd,

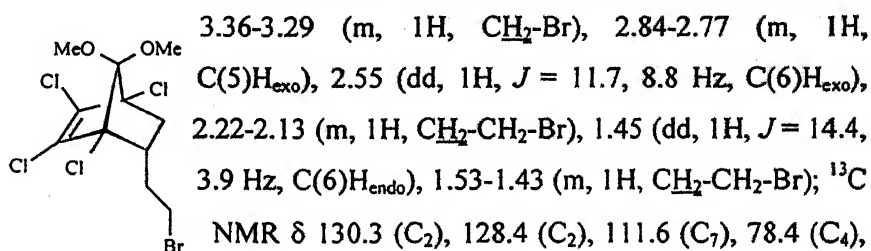


1H,  $J = 8.8, 3.6$  Hz), 3.84 (s, 3H, OMe), 3.83 (d, 1H,  $J = 8.5$  Hz), 3.66 (s, 3H, OMe), 3.61 (s, 3H, OMe), 2.94 (ddd, 1H,  $J = 11.0, 2.2, 3.6$  Hz), 2.66 (dd, 1H,  $J = 12.7, 11.0$  Hz), 1.85 (dd, 1H,  $J = 12.7, 2.2, 3.6$  Hz);  $^{13}C$  NMR  $\delta$  196.7 (C=O),

105.1, 102.1, 76.0, 74.2, 72.3, 54.9, 52.4, 51.4, 46.8, 36.1; IR (KBr) 2950, 1770, 1430, 1190, 1070  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{O}_3$ : C 44.47, H 4.75; Found C 44.52, H 4.71.

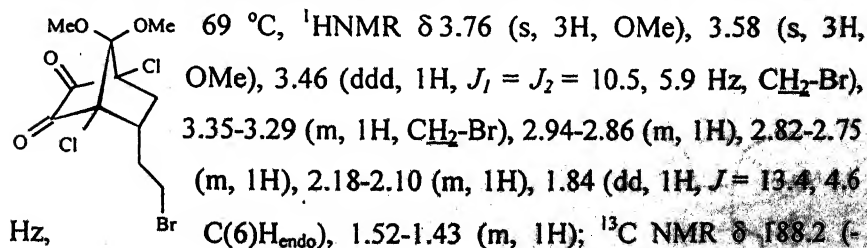
**5-(2-Bromo-ethyl)-1,2,3,4-tetrachloro-7,7-dimethoxy-**

**bicyclo[2.2.1]hept-2-ene 3r**: Yield: 91%; viscous liquid;  $^1\text{H}$ NMR  $\delta$  3.61 (s, 3H, OMe), 3.55 (s, 3H, OMe), 3.48-3.41 (m, 1H,  $\text{CH}_2\text{-Br}$ ),



**5-(2-Bromo-ethyl)-1,4-dichloro-7,7-dimethoxy-**

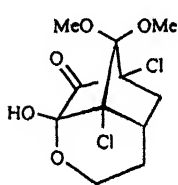
**bicyclo[2.2.1]heptane-2,3-dione 1r**: Yield: 94%; yellow solid; mp 67-



C=O), 187.8 (-C=O), 102.3 (C<sub>7</sub>), 79.5 (C<sub>4</sub>), 74.9 (C<sub>1</sub>), 52.7 (OMe), 52.1 (OMe), 40.6, 37.3, 32.4, 29.7; IR (KBr) 2900, 1770, 1440, 1280 cm<sup>-1</sup>; Anal. Calcd. for C<sub>11</sub>H<sub>13</sub>Cl<sub>2</sub>O<sub>4</sub>: C, 47.16; H, 4.68; Found: C, 47.20; H, 4.70.

**1,8-Dichloro-3-hydroxy-9,9-dimethoxy-4-oxa-**

**tricyclo[5.2.1.0<sup>3,8</sup>]decan-2-one 140:** Yield: 93%; colorless solid; mp 161 °C, <sup>1</sup>HNMR δ 4.02-3.97 (tdd, 1H, *J* = 12.7, 5.3, 1.4 Hz, -O-



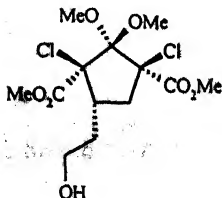
CH<sub>2</sub>), 3.68 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.61-3.54 (m, 1H), 3.00-2.96 (m, 1H), 2.62 (dd, 1H, *J*<sub>1</sub> = *J*<sub>2</sub> = 12.7 Hz, C(8)H<sub>exo</sub>), 2.20-2.11 (m, 1H), 1.78 (dd, 1H, *J* = 12, 3.9 Hz, C(8)H<sub>endo</sub>), 1.39-1.33 (m, 1H); <sup>13</sup>C

NMR δ 201.7 (-C=O), 103.0 (C<sub>9</sub>), 95.7 (C<sub>3</sub>), 75.6 (bridgehead), 73.4 (bridgehead), 60.6 (-O-CH<sub>2</sub>-), 52.0 (OMe), 51.4 (OMe), 37.2, 33.4, 22.2; IR (neat) 3300, 2900, 1770, 1460, 1420, 1200 cm<sup>-1</sup>; Anal. Calcd. for C<sub>11</sub>H<sub>14</sub>Cl<sub>2</sub>O<sub>5</sub>: C, 44.47; H, 4.75; Found: C, 44.51; H, 4.79.

**1,3-Dichloro-4-(2-hydroxy-ethyl)-2,2-dimethoxy-cyclopentane-1,3-**

**dicarboxylic acid dimethyl ester 141:** Yield: 14%; viscous liquid;

<sup>1</sup>HNMR δ 3.82 (s, 3H, CO<sub>2</sub>Me), 3.80 (s, 3H, CO<sub>2</sub>Me), 3.80-3.69 (m, 1H), 3.69 (s, 3H, OMe), 3.31 (dd, 1H, *J*<sub>1</sub> = *J*<sub>2</sub>



=14.0 Hz, C(5)H<sub>β</sub>), 3.21 (s, 3H, OMe), 2.94-2.86 (m, 1H), 2.22 (dd, 1H, *J* = 14.4, 5.9 Hz, C(5)H<sub>α</sub>), 1.98-1.90 (m, 1H), 1.67-1.57 (m, 2H);

$^{13}\text{C}$  NMR  $\delta$  168.3 (-O-C=O), 167.8 (-O-C=O), 110.7 ( $\text{C}_7$ ), 81.3, 79.0, 60.9 (- $\text{CH}_2\text{-OH}$ ), 53.5 (OMe), 53.3 (OMe), 52.3 (OMe), 52.4 (OMe), 47.3, 42.6, 31.6; IR (neat) 3400, 2900, 1720, 1430, 1260  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{13}\text{H}_{20}\text{Cl}_2\text{O}_7$ : C, 43.47; H, 5.61; Found: C, 43.51; H, 5.66.

**6,7a-Dichloro-7,7-dimethoxy-1-oxo-octahydro-cyclopenta[c]pyran-6-carboxylic acid methyl ester 142:** Yield: 81%; colorless solid; mp

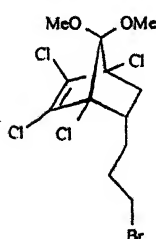
128-130  $^\circ\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  4.48 (dt, 1H,  $J = 11.9, 1.9$  Hz, -O- $\text{CH}_2$ ), 4.42-4.37 (m, 1H, -O- $\text{CH}_2$ ), 3.86 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.78 (s, 3H, OMe), 3.30 (s, 3H, OMe), 3.31-3.29 (m, 1H, merged with OMe), 2.84 (dd, 1H,  $J = 14.2, 12.0$  Hz,  $\text{H}_a$ ), 2.38-2.30 (m, 1H), 2.27 (dd, 1H,  $J = 14.2, 7.8$  Hz,  $\text{H}_b$ ), 1.72-1.67 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  168.2 (-O-C=O), 166.9 (-O-C=O), 111.1 ( $\text{C}_7$ ), 73.8, 73.4, 65.2 (-O- $\text{CH}_2$ -), 53.8 (OMe), 52.1 (OMe), 44.3, 38.8, 25.0; IR (neat) 2900, 1760, 1720, 1440, 1300  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{12}\text{H}_{16}\text{Cl}_2\text{O}_6$ : C, 44.06; H, 4.93; Found: C, 44.01; H, 4.90.

**6-Hydroxy-7,7-dimethoxy-1-oxo-octahydro-cyclopenta[c]pyran-6-carboxylic acid methyl ester 143:** Yield: 71%; viscous liquid;  $^1\text{H}$ NMR

$\delta$  3.87 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.83-3.76 (m, 1H), 3.71-3.66 (m, 1H), 3.61 (s, 3H, OMe), 3.39 (s, 3H, OMe), 2.98 (dd, 1H,  $J = 13.14, 10.4$  Hz), 2.83-2.76 (m, 1H), 2.04-1.96 (m, 1H), 1.82 (dd, 1H,  $J = 13.2, 4.5$  Hz), 1.34-1.26 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  167.7 (-O-C=O), 166.2 (-O-C=O), 108.8 ( $\text{C}_7$ ), 84.8 ( $\text{C}_6$ ), 76.0 (-C-Cl), 60.1 (-O- $\text{CH}_2$ -), 53.2 (OMe), 51.8 (OMe), 51.6

(OMe), 37.8, 37.5, 33.0; IR (neat) 3300, 2900, 1770, 1700, 1420, 1300  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{12}\text{H}_{17}\text{ClO}_7$ : C, 46.69; H, 5.55; Found: C, 46.73; H, 5.58.

**5-(3-Bromo-propyl)-1,2,3,4-tetrachloro-7,7-dimethoxy-bicyclo[2.2.1]hept-2-ene 3s:** Yield: 94%; viscous liquid;  $^1\text{H}$  NMR

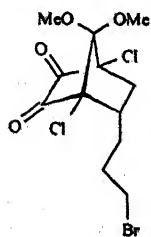


$\delta$  3.60 (s, 3H, OMe), 3.55 (s, 3H, OMe), 3.42-3.33 (m, 2H), 2.60-2.53 (m, 1H), 2.48 (dd, 1H,  $J = 11.2, 8.8$  Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 1.89-1.80 (m, 3H), 1.45 (dd, 1H,  $J = 11.2, 3.7$  Hz,  $\text{C}(6)\text{H}_{\text{endo}}$ ), 1.06-0.97 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  129.9, 128.5, 111.7 ( $\text{C}_7$ ), 78.8 ( $\text{C}_4$ ), 74.5 ( $\text{C}_1$ ), 52.6

(OMe), 51.5 (OMe), 46.5, 41.6, 32.8, 30.5, 28.6; IR (neat) 2900, 1600, 1420, 1260, 1200  $\text{cm}^{-1}$ .

The Diels-Alder adducts **2g**, **3r** and **3s** were prepared similar to that discussed under Chapter-1A (Table 1A.1, page 204).

**5-(3-Bromo-propyl)-1,4-dichloro-7,7-dimethoxy-bicyclo[2.2.1]heptane-2,3-dione 1s:** Yield: 98%; yellow solid; mp 77

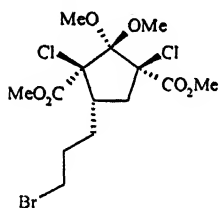


$^{\circ}\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  3.73 (s, 3H, OMe), 3.57 (s, 3H, OMe), 3.39-3.31 (m, 2H), 2.79 (dd, 1H,  $J_1 = J_2 = 12.4$  Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 2.68 (tt, 1H,  $J = 11.6, 4.1$  Hz), 1.91-1.72 (m, 4H), 1.11-1.00 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  188.2 ( $-\text{C}=\text{O}$ ), 188.1 ( $-\text{C}=\text{O}$ ), 102.5 ( $\text{C}_7$ ), 80.0 ( $\text{C}_4$ ), 75.0 ( $\text{C}_1$ ), 52.7



(OMe), 52.1 (OMe), 41.4, 37.8, 32.1, 30.2, 28.6; IR (KBr) 2900, 1780, 1460, 1280, 1200  $\text{cm}^{-1}$ . Anal. Calcd. for  $\text{C}_{12}\text{H}_{15}\text{Cl}_2\text{O}_4$ : C, 49.00; H, 5.14; Found: C, 48.96; H, 5.11.

**4-(3-Bromo-propyl)-1,3-dichloro-2,2-dimethoxy-cyclopentane-1,3-dicarboxylic acid dimethyl ester 50s:** Yield: 56%; colorless solid, mp 110  $^{\circ}\text{C}$ ;  $^1\text{H}$ NMR  $\delta$  3.82 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.81 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.68 (s,



3H, OMe), 3.41-3.37 (m, 2H), 3.30 (dd, 1H,  $J_1 = J_1 = 14.0$  Hz,  $\text{C}(5)\text{H}_\beta$ ), 3.21 (s, 3H, OMe), 2.76-2.68 (m, 1H), 2.14 (dd, 1H,  $J = 14.4, 5.8$  Hz,  $\text{C}(5)\text{H}_\alpha$ ), 1.98-1.79 (m, 3H), 1.53-1.42 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  168.2 ( $-\text{O}-\text{C}=\text{O}$ ), 167.6 ( $-\text{O}-\text{C}=\text{O}$ ),

110.7 ( $\text{C}_7$ ), 81.1, 78.0, 53.44 (OMe), 53.35 (OMe), 53.3 (OMe), 52.4 (OMe), 49.5, 42.3, 33.1, 30.9, 27.1; IR (KBr) 2850, 1710, 1420, 1250, 1190  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{14}\text{H}_{21}\text{BrCl}_2\text{O}_6$ : C, 38.56; H, 4.85; Found: C, 38.59; H, 4.87.

## Chapter 2

## A Concise Synthesis of Novel Oxabridged Compounds

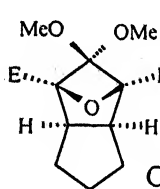
**Tetramethyl 2,2,6,6-tetramethoxyhexahydro-1,3:5,7-diepoxy-s-indacene-1,3,5,7-tetracarboxylate 162.** To a solution of the major bis-lactone **158** (38 mg, 0.069 mmol) in MeOH (0.5 ml) was added a solution of NaOH (3.75 mmol, 150mg) in H<sub>2</sub>O (1 ml). The mixture was refluxed for 24 h. 5% HCl (10 ml) was added and extracted with ethyl acetate (3×5 ml). The combined ethyl acetate layer was washed once with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude carboxylic acid obtained after concentration of ethyl acetate layer was treated with excess diazomethane in ether:methanol (1:1) at 0°C. After quenching excess diazomethane with acetic acid, the solution was concentrated and silica gel column chromatography (50% ethyl acetate-hexane) afforded the pure product **162** (17.6 mg) in 46% yield in two steps. Yield: 46%; colorless flakes, mp 250 °C; <sup>1</sup>H NMR δ 3.80 (s, 12H, CO<sub>2</sub>Me), 3.43 (s,

6H, OMe), 3.31 (s, 6H, OMe), 2.76-2.73 (m, 4H), 1.44-1.36 (m, 4H); <sup>13</sup>C NMR δ 166.5 (O-C=O), 110.2, 91.6, 52.6 (CO<sub>2</sub>Me), 52.0 (OMe), 51.7 (OMe), 40.1, 16.8; IR (KBr) 2900, 1730, 1420, 1220, 1100 cm<sup>-1</sup>; Anal. calcd. for C<sub>24</sub>H<sub>32</sub>O<sub>14</sub>: C 52.94, H 5.92; Found: C 52.85, H 5.89.

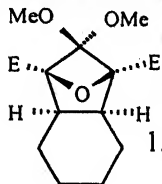
**General procedure for the preparation of oxa-bridge derivatives from bridged lactones:** To a solution of the lactones (0.2 mmol) in

MeOH (2 ml) was added a solution of NaOH (6 mmol) in H<sub>2</sub>O (1 ml). The mixture was refluxed for specified time. 5% HCl (10 ml) was added and extracted with ethyl acetate (3×5 ml). The combined ethyl acetate layer was washed once with brine and dried over Na<sub>2</sub>SO<sub>4</sub>. The crude carboxylic acid obtained after concentration of ethyl acetate layer was treated with excess diazomethane in ether:methanol (1:1) at 0 °C. After quenching excess diazomethane with acetic acid, the solution was concentrated and silica gel column chromatography (ethyl acetate-hexane) afforded the pure product.

**Oxabridge derivarive 163i:** Yield: 88%; colorless solid, mp 48-50°C (dec); <sup>1</sup>H NMR δ 3.82 (s, 6H, CO<sub>2</sub>Me), 3.45 (s, 3H, OMe), 3.32 (s, 3H, OMe), 3.14 (br s, 2H), 1.76-1.74 (m, 1H), 1.68-1.66 (m, 1H), 1.44-1.33 (m, 1H), 1.29-1.25 (m, 1H); <sup>13</sup>C NMR δ 167.0 (O-C=O), 113.9, 91.1, 52.3 (2C, CO<sub>2</sub>Me), 51.7 (OMe), 51.6 (OMe), 49.0 (2C), 28.5, 25.8 (2C); IR (KBr) 2900, 1720, 1440, 1360 cm<sup>-1</sup>; Anal. calcd. for C<sub>14</sub>H<sub>20</sub>O<sub>7</sub>: C 55.99, H 6.71; Found: C 55.53, H 6.78.

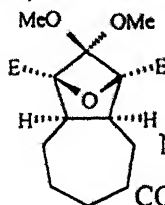


**Dimethyl 10,10-Dimethoxy-9-oxa-tricyclo[6.1.1.0<sup>2,7</sup>]decane-1,8-dicarboxylate 163j:** Yield: 90%; colorless solid, mp 58-60°C (dec); <sup>1</sup>H NMR δ 3.81 (s, 6H, CO<sub>2</sub>Me), 3.46 (s, 3H, OMe), 3.33 (s, 3H, OMe), 2.72-2.70 (m, 2H), 1.69 (m, 2H), 1.40-1.36 (m, 6H); <sup>13</sup>C NMR δ 167.0 (2C, O-C=O), 110.2, 92.2



(2C), 52.3 (2C, CO<sub>2</sub>Me), 52.0 (OMe), 51.7 (OMe), 41.8 (2C), 17.9 (2C), 17.6 (2C); IR (KBr) 2850, 1700, 1430, 1000 cm<sup>-1</sup>; Anal. calcd. for C<sub>15</sub>H<sub>22</sub>O<sub>7</sub>: C 57.32, H 7.05; Found: C 57.53, H 7.14.

**Oxabridge derivarive 163k:** Yield: 93%; colorless solid, mp 98-100 °C; <sup>1</sup>H NMR δ 3.81 (s, 6H, CO<sub>2</sub>Me), 3.47 (s, 3H, OMe), 3.32 (s, 3H,



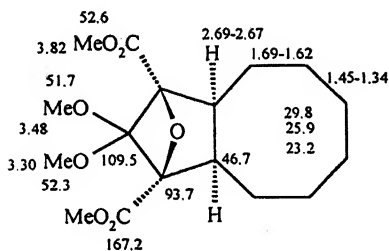
OMe), 2.84-2.81 (m, 2H), 1.93-1.73 (br s, 2H), 1.80-1.73 (m, 1H), 1.60-1.45 (m, 4H), 1.21-1.18 (m, 3H); <sup>13</sup>C

NMR δ 166.9 (2C, O-C=O), 110.3, 92.5, 52.2 (2C, CO<sub>2</sub>Me), 51.7 (OMe), 51.6(OMe), 47.9 (2C), 31.0, 28.9

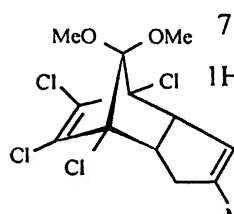
(2C), 25.8 (2C); IR (KBr) 2850, 1700, 1430, 1360, 1340 cm<sup>-1</sup>; Anal. calcd. for C<sub>16</sub>H<sub>24</sub>O<sub>7</sub>: C 58.53, H 7.37; Found: C 58.56, H 7.40.

**Dimethyl 12,12-Dimethoxy-11-oxa-tricyclo[8.1.1.0<sup>2,9</sup>]dodecane-1,10-dicarboxylate 163l:** Refluxing the bicyclic lactone **51l** (96 mg, 0.28 mmol) with NaOH (331 mg, 8.28mmol in 1ml water) in MeOH for 20hr and treatment of the resulting crude carboxylic acid in CH<sub>2</sub>N<sub>2</sub>, as described above, furnished the oxa-bridge compound **163l** (87 mg). Yield: 92%; colorless solid, mp 119-121 °C; <sup>1</sup>H NMR δ 3.82 (s, 6H, CO<sub>2</sub>Me), 3.48 (s, 3H, OMe), 3.30 (s, 3H, OMe), 2.69-2.67 (m, 2H), 1.69-1.62 (m, 4H), 1.45-1.34 (m, 8H); <sup>13</sup>C NMR δ 167.2 (2C, O-C=O), 109.5, 93.7 (2C), 52.2 (2C, CO<sub>2</sub>Me), 51.9 (OMe), 51.6 (OMe), 46.7 (2C), 29.8 (2C), 25.9 (2C), 23.2 (2C); IR (KBr) 2850, 1710, 1430, 1100

$\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{17}\text{H}_{26}\text{O}_7$ : C 59.64, H 7.65; Found: C 59.73, H 7.51.

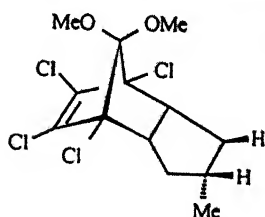


**Methyl cyclopentadiene adduct 165:** To a stirred solution of 6.24 gm of freshly cracked methyl cyclopentadiene was slowly added to a mixture of 7 gms of tetrachlorodimethoxy cyclopentadiene and a catalytic hydroquinone in 4 ml of toluene at room temperature. After 1 h stirring at room temperature, the mixture was then refluxed for 1 h (till the completion of starting material). The toluene and excess methyl cyclopentadiene was distilled off under reduced pressure and the residue was subjected to silica gel column chromatography with 20:1 hexane:EtOAc furnished the adduct **165** (6.35 g, 71%). Yield:



71%; colorless solid, mp  $96^\circ\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  5.17 (s, 1H, olefinic), 3.63-3.61(m, 1H), 3.60 (s, 3H, OMe), 3.54 (s, 3H, OMe), 3.22 (dt, 1H,  $J = 9.0, 3.4$  Hz), 2.30 (1/2 of AB quartet, 1H,  $J = 17.7, 9.5$  Hz), 2.15 (d, 1H,  $J = 17.7$  Hz), 1.67 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  145.6, 129.6, 127.1, 119.8, 113.5, 78.5, 78.0, 61.2; 52.4 (OMe), 51.5 (OMe), 49.4 (2C), 35.9, 16.7; IR (KBr) 2900, 1600, 1440, 1200  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{13}\text{H}_{14}\text{Cl}_4\text{O}_2$ : C 45.3, H 4.10; Found: C 45.45, H 4.04.

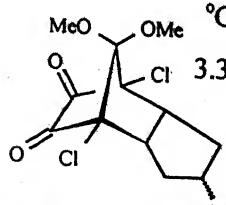
**Tetrachloro derivative 166:** A mixture of the adduct 165 (550 mg, 1.59 mmol) and 10% palladium-charcoal (*ca* 8 mg) and  $\text{PtO}_2$  (*ca* 4 mg) was stirred under an atmosphere of hydrogen (a balloon) till the absorption of hydrogen ceases. Filtration of the reaction mixture through a small pad of silical gel column afforded the pure product (531 mg, 96%). Yield: 96%; colorless solid, mp  $50^\circ\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  3.58



(s, 3H, OMe), 3.54 (s, 3H, OMe), 3.09-3.02 (m, 2H), 1.94-1.84 (m, 3H), 0.96 (d, 3H,  $J = 5.8$  Hz, Me), 0.78-0.70 (m, 2H);  $^{13}\text{C}$  NMR  $\delta$  129.7 (2C), 115.5, 78.1 (2C, bridgehead), 53.8 (2C), 52.4 (OMe), 51.5 (OMe), 36.6, 34.3 (2C), 18.9 (Me);

IR (KBr) 2850, 1600, 1440,  $1260\text{ cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{13}\text{H}_{16}\text{Cl}_4\text{O}_2$ : C 45.12, H 4.66; Found: C 45.37, H 4.58.

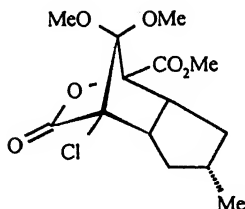
**$\alpha$ -diketone 167:** Prepared following the general procedure. Yield: 98%; yellow solid (directly crystallized without a column), mp  $123\text{-}124^\circ\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  3.73 (s, 3H, OMe), 3.55 (s, 3H, OMe),



3.32-3.19 (m, 2H), 2.03-1.94 (m, 3H), 0.95 (d, 3H,  $J = 5.8$  Hz, Me), 0.61-0.56 (m, 2H);  $^{13}\text{C}$  NMR  $\delta$  188.9 ( $-\text{C}=\text{O}-$ , 2C), 105.7, 79.4 (2C, bridgehead), 52.4 (OMe), 52.0 (OMe), 48.8 (2C), 36.7, 35.0 (2C), 18.2 (Me); IR (KBr) 2850, 1750, 1440,  $1210\text{ cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{13}\text{H}_{16}\text{Cl}_2\text{O}_4$ : C 50.83, H 5.25; Found: C 50.93, H 5.30.

**The bridged lactone 168:** Yield: 93%; colorless solid, mp 124-126 °C;

$^1\text{H}$  NMR  $\delta$  3.85 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.61 (s, 3H, OMe), 3.46 (q, 1H,  $J =$



10 Hz), 3.61 (s, 3H, OMe), 3.04 (q, 1H,  $J =$

10 Hz), 2.02-1.95 (m, 2H), 1.80-1.74 (m, 1H),

1.21-1.12 (m, 1H), 1.00 (d, 3H,  $J = 4.9$  Hz,

Me), 0.88-0.79 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  168.0 (-

O-C=O), 166.2 (-O-C=O), 111.9, 85.6

(bridgehead, C- $\text{CO}_2\text{Me}$ ), 76.3 (bridgehead, C-Cl), 53.1 ( $\text{CO}_2\text{Me}$ ), 51.64

(OMe), 51.61 (OMe), 48.6, 47.6, 36.9, 35.2, 31.7, 18.4; IR (KBr) 2900,

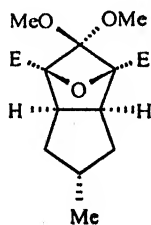
1800, 1730, 1460, 1300  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{14}\text{H}_{19}\text{ClO}_6$ : C 52.75, H

6.01; Found: C 52.80, H 5.98.

**The oxo-bridge derivative 169:** Yield: 83%; viscous liquid;  $^1\text{H}$  NMR

$\delta$  3.81 (s, 6H,  $\text{CO}_2\text{Me}$ ), 3.44 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.16-

3.09 (m, 2H), 1.98-1.84 (m, 1H), 1.81-1.75 (m, 2H), 1.00 (d, 3H,  $J =$



6.4 Hz, Me), 0.98-0.92 (m, 2H, merged with Me

doublet);  $^{13}\text{C}$  NMR  $\delta$  167.2 (2C, O-C=O), 113.8,

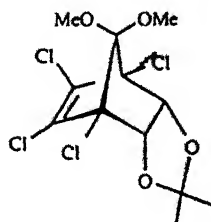
90.6 (2C), 52.4 (2C,  $\text{CO}_2\text{Me}$ ), 51.9 (OMe), 51.8

(OMe), 49.2 (2C), 37.5, 33.7 (2C), 18.5 (Me); IR

(KBr) 2850, 1700, 1430, 1360, 1340  $\text{cm}^{-1}$ ; Anal.

calcd. for  $\text{C}_{15}\text{H}_{22}\text{O}_7$ : C 57.32, H 7.05, Found: C 57.56, H 7.08.

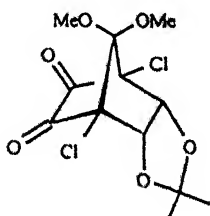
**Acetonide 3p:** Yield: 80% in two steps from adduct 3n. colorless solid,



mp 100-102 °C;  $^1\text{H}$  NMR  $\delta$  4.84 (s, 2H), 3.59 (s, 3H, OMe), 3.56 (s, 3H, OMe), 1.40 (s, 3H, Me), 1.33 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  129.7 (2C), 115.5, 114.2, 85.6 (2C), 77.4 (2C, bridgehead), 52.4 (OMe), 51.8 (OMe), 25.6 (Me), 25.5 (Me); IR

(KBr) 2900, 1590, 1440, 1360, 1320  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{12}\text{H}_{14}\text{Cl}_4\text{O}_4$ : C 39.59, H 3.88; Found: C 39.62, H 3.84.

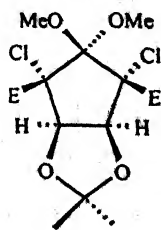
**$\alpha$ -diketone 1p:** Yield: 95%; yellow solid (dichloro methane-hexane),



mp 138-140 °C;  $^1\text{H}$  NMR  $\delta$  4.94 (s, 2H), 3.66 (s, 3H, OMe), 3.48 (s, 3H, OMe), 1.25 (s, 3H, Me), 1.24 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  184.4 ( $-\text{C}=\text{O}$ , 2C), 115.7, 105.2, 82.0 (2C), 78.0 (2C, bridgehead), 52.5 (OMe), 52.4 (OMe), 25.2 (Me), 23.9 (Me);

IR (KBr) 2900, 1780, 1750, 1360, 1200  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{12}\text{H}_{14}\text{Cl}_2\text{O}_6$ : C 44.33, H 4.34; Found: C 44.30, H 4.36.

**Cyclopentane diester 50p:** Yield: 33%; colorless solid, mp 131-133

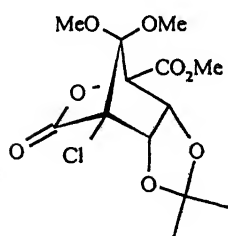


°C;  $^1\text{H}$  NMR  $\delta$  5.02 (s, 2H), 3.81 (s, 6H,  $\text{CO}_2\text{Me}$ ), 3.80 (s, 3H, OMe), 3.54 (s, 3H, OMe), 1.37 (s, 3H, Me), 1.30 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  166.1 (2C,  $\text{O}-\text{C}=\text{O}$ ), 112.2, 108.9, 85.4, 72.3, 52.4 (OMe), 52.73 (2C, OMe), 52.66 (OMe), 25.3 (Me), 25.8 (Me); IR



(KBr) 2900, 1740, 1420, 1360, 1300  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{14}\text{H}_{20}\text{Cl}_2\text{O}_8$ : C 43.43, H 5.21; Found: C 43.47, H 5.10.

**Lactone 51p**: Yield: 91%; colorless solid, mp 154-156  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  5.37 (d, 1H,  $J = 7.4$  Hz), 4.87 (d, 1H,  $J = 7.4$  Hz), 3.91 (s, 3H,



$\text{CO}_2\text{Me}$ ), 3.61 (s, 3H, OMe), 3.40 (s, 3H, OMe),

1.49 (s, 3H, Me), 1.37 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$

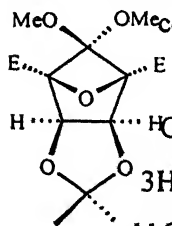
164.5 (2C,  $-\text{O}-\text{C}=\text{O}$ ), 116.3, 111.0, 83.6, 81.0,

80.3, 51.5 (OMe), 52.0 (OMe), 25.5 (Me), 25.3

(Me); IR (KBr) 2900, 1800, 1730, 1430, 1360

$\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{13}\text{H}_{17}\text{ClO}_8$ : C 46.37, H 5.09; Found: C 46.40, H 5.11.

**Oxa-bridge derivative 170**: The bicyclic lactone 51p (65 mg, 0.205 mmol) with NaOH (246 mg, 6.15 mmol in 1ml water) in MeOH was refluxed for 20hr and the resulting crude carboxylic acid was treated with  $\text{CH}_2\text{N}_2$ , as described above, giving rise to the oxa-bridge compound 170 (57 mg). Yield: 83%; colorless solid, mp



118-120  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  5.12 (s, 2H), 3.86 (s, 6H,

$\text{HCO}_2\text{Me}$ ), 3.41 (s, 3H, OMe), 3.33 (s, 3H, OMe), 1.51 (s,

3H, Me), 1.37 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  164.9 (2C,  $\text{O}-\text{C}=\text{O}$ ),

116.2, 114.2, 89.3, 82.1, 52.8 (2C,  $\text{CO}_2\text{Me}$ ), 51.91 (OMe),

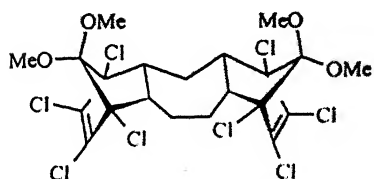
51.86 (OMe), 26.4 (Me), 25.8 (Me); IR (KBr) 2850, 1710, 1440, 1360, 1300, 1200  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{14}\text{H}_{20}\text{O}_9$ : C 50.60, H 6.07; Found: C 50.64, H 6.10.

**One pot synthesis of tetramethyl 2,2,6,6-tetramethoxyhexahydro-1,3:5,7-diepoxy-*s*-indacene-1,3,5,7-tetracarboxylate 162 from bis- $\alpha$ -diketone 157:** To a stirred solution of diketone 157 (90mg, 0.17 mmol) in THF (2ml) and methanol (2 ml) was added 30%  $\text{H}_2\text{O}_2$  (0.22 ml) followed by slow addition of 6N NaOH solution (0.1ml). After stirring at room temperature ( $\sim 20^\circ\text{C}$ ) for 2 h, a solution of NaOH (408 mg, 10.2 mmol) in  $\text{H}_2\text{O}$  (1 ml) was added. The mixture was refluxed for 20 h, cooled and 10 % HCl (7 ml) was added and extracted with ethyl acetate (3 $\times$ 5 ml). The combined ethyl acetate layer was washed once with brine and dried over  $\text{Na}_2\text{SO}_4$ . The crude carboxylic acid obtained after concentration of ethyl acetate layer was treated with excess diazomethane in ether:methanol (1:1) at  $0^\circ\text{C}$ . After quenching excess diazomethane with acetic acid, the solution was concentrated and silica gel column chromatography (50% ethyl acetate-hexane) afforded the pure product in 60% of yield.

**Bis-adduct 171:** It was prepared by using literature procedure.<sup>58</sup> Yield: 77%; colorless solid, mp  $212^\circ\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  5.55 (s, 2H), 3.60 (s, 6H, OMe), 3.39 (d, 2H,  $J = 11.2$  Hz), 2.74-2.67 (m, 2H), 2.03 (dt,  $J = 13.1$ , 2.0 Hz), 0.74 (q,  $J = 12.8$  Hz);  $^{13}\text{C}$  NMR  $\delta$  129.2 (2C), 129.0 (2C),

125.8 (2C), 111.4 (2C), 78.7 (2C), 77.7 (2C), 52.7 (2C), 51.6 (2C), 49.1 (2C), 48.6 (2C), 20.9; IR (KBr) 2900, 1600, 1440  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{21}\text{H}_{20}\text{Cl}_8\text{O}_4$ : C 40.68, H 3.25; Found: C 40.71, H 3.27.

**Compound 172:** A mixture of the bisadduct 171 (550 mg, 0.89 mmol) in dry ethylacetate (5 ml) was shaken in a Parr hydrogenation apparatus over 10% palladium-charcoal (*ca* 12 mg) and  $\text{PtO}_2$  (*ca* 6 mg) at a hydrogen pressure of 50 psi. for 30 h. The catalyst was filtered off and



solvent removed to furnish the pure product 172 (537mg, 97%). Yield:

97%; colorless solid, mp 190-192  $^{\circ}\text{C}$ ;

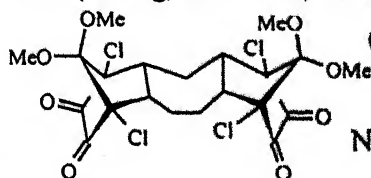
$^1\text{H}$  NMR  $\delta$  3.58 (s, 6H, OMe), 3.53

(s, 6H, OMe), 2.77-2.69 (m, 4H), 2.05 (d, 1H,  $J = 13.9$  Hz), 1.77-1.72 (m, 2H), 1.57-1.49 (m, 2H), 1.00-0.85 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  129.1 (2C),

128.9 (2C), 111.4 (2C), 79.5 (2C), 79.1 (2C), 52.7 (2C), 51.6 (2C), 50.4 (2C), 46.8 (2C), 22.6 (2C), 21.3; IR (KBr) 2900, 1600, 1440, 1270,

1200  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{21}\text{H}_{22}\text{Cl}_8\text{O}_4$ : C 40.55, H 3.56; Found: C 40.58, H 3.54.

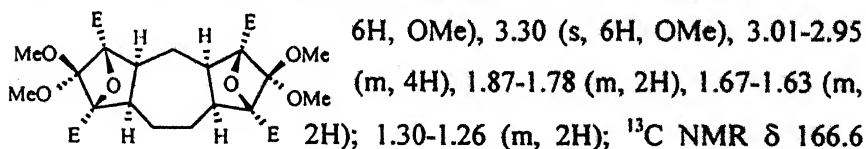
**Bis  $\alpha$ -diketone 173:** To a vigorously stirred solution of the bis-adduct 172 (311mg, 0.5 mmol) in acetonitrile (6 ml) and  $\text{CCl}_4$  (6 ml) at  $0^{\circ}\text{C}$



(ice-water bath) was added a solution of  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$  (15.7 mg, 0.06 mmol) and  $\text{NaIO}_4$  (299.6 mg, 1.4 mmol) in water

(1 ml). The mixture was stirred for 30 h and continuously monitored by tlc. The resulting suspension was filtered through a thin pad of silica gel, which was then washed with  $\text{CH}_2\text{Cl}_2$  and ethyl acetate (40 ml, 1:1). Concentration of the filtrate followed by washing the resulting yellow crystalline product in hexane (10 ml) gave the pure bis-diketone 174 (264 mg, 97%). Yield: 97%, yellow solid, mp 260 °C;  $^1\text{H}$  NMR  $\delta$  3.73 (s, 6H, OMe), 3.54 (s, 6H, OMe), 2.93-2.85 (m, 4H), 2.06-2.02 (m, 2H), 1.84-1.79 (m, 2H), 1.28-1.24 (m, 2H), 0.72-0.62 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  187.4 (2C,  $-\text{C}=\text{O}$ ), 187.3 (2C,  $-\text{C}=\text{O}$ ), 101.6 (2C), 80.2 (2C), 79.5 (2C), 52.8 (2C), 52.1 (2C), 46.2 (2C), 42.2 (2C), 22.0 (2C), 20.7; IR (KBr) 2900, 1750, 1450, 1200  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{21}\text{H}_{22}\text{Cl}_4\text{O}_8$ : C 46.35, H 4.07; Found: C 46.38, H 4.09.

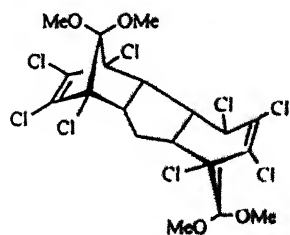
**Bis oxa-bridged derivative 175:** Yield: 71%; colorless solid, mp 128-130 °C;  $^1\text{H}$  NMR  $\delta$  3.80 (s, 6H,  $\text{CO}_2\text{Me}$ ), 3.78 (s, 6H,  $\text{CO}_2\text{Me}$ ), 3.46 (s,



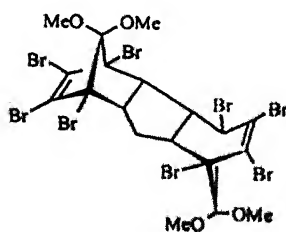
(2C,  $\text{O}-\text{C}=\text{O}$ ), 166.4 (2C,  $\text{O}-\text{C}=\text{O}$ ), 109.9 (2C), 92.9 (2C), 92.1 (2C), 52.4 (2C,  $\text{CO}_2\text{Me}$ ), 52.3 (2C,  $\text{CO}_2\text{Me}$ ), 51.8 (2C, OMe), 51.7 (2C, OMe), 46.2 (2C), 42.6 (2C), 23.0 (2C), 21.9; IR (KBr) 2900, 1720, 1420, 1220, 1190  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{25}\text{H}_{34}\text{O}_{14}$ : C 53.76, H 6.14; Found: C 53.80, H 6.16.

Preparation of 2:1 adducts of 5,6 with cyclopentadiene: The tetrahalo cyclopentadiene monoadducts 130a and 130b was further treated with 1 equivalent of 5 and 6 respectively in benzene in a sealed tube for 48 h to furnish the *endo,anti,endo*- adducts 177a and 177b

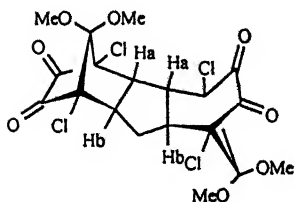
**Bis adduct 177a:** Yield: 80%; colorless solid, mp 232-234 °C;  $^1\text{H}$  NMR  $\delta$  3.57 (s, 6H, OMe), 3.51 (s, 6H, OMe), 3.13 (dd, 2H,  $J = 15.6$ , 7.8 Hz), 2.99 (d, 2H,  $J = 7.8$  Hz), 1.77 (t, 2H,  $J = 7.8$  Hz);  $^{13}\text{C}$  NMR  $\delta$  130.0 (2C), 129.2 (2C), 114.5 (2C), 77.9 (2C), 77.1 (2C), 56.3 (2C), 54.6 (2C), 52.5 (2C), 51.6 (2C), 24.4, IR (KBr) 2900, 1600, 1420, 1330, 1280, 1260  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{19}\text{H}_{18}\text{Cl}_4\text{O}_4$ : C 38.42, H 3.05; Found C 38.40, H 3.07.



**Bis adduct 177b:** Yield: 71% (57% based on starting material); colorless solid, mp 248-250 °C (dec);  $^1\text{H}$  NMR  $\delta$  3.60 (s, 6H, OMe), 3.56 (s, 6H, OMe), 3.25 (dd, 2H,  $J = 15.5$ , 7.8 Hz), 3.17 (d, 2H,  $J = 7.8$  Hz), 1.88 (t, 2H,  $J = 7.6$  Hz);  $^{13}\text{C}$  NMR  $\delta$  126.0 (2C), 125.2 (2C), 114.5 (2C), 71.4 (2C), 71.1 (2C), 57.2 (2C), 55.8 (2C), 52.8 (2C), 51.6 (2C), 24.6; IR (KBr) 2900, 1580, 1420, 1330, 1280, 1260  $\text{cm}^{-1}$ . Anal. calcd. for  $\text{C}_{19}\text{H}_{18}\text{Br}_4\text{O}_4$ : C 24.03, H 1.91; Found: C 24.07, H 1.91

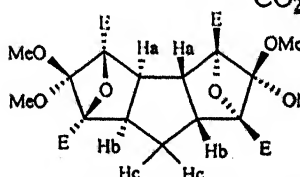


**Bis  $\alpha$ -diketone 178:** Yield: 95%; yellow solid, mp 258-260 °C;  $^1\text{H}$  NMR  $\delta$  3.68 (s, 6H, OMe), 3.54 (s, 6H, OMe), 3.19 (dd, 2H,  $J$  = 16.4, 10.7 Hz), 2.89 (d, 2H,  $J$  = 10.7 Hz), 1.66 (t, 2H,  $J$  = 8.2 Hz);  $^{13}\text{C}$  NMR  $\delta$  188.1 (2C, -C=O), 187.7 (2C, -C=O), 104.3 (2C), 79.2 (2C), 78.3 (2C), 52.7 (2C, OMe), 52.3 (2C, OMe), 50.5 (2C), 50.4 (2C), 24.4; IR (KBr)



2900, 1740, 1440  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{19}\text{H}_{18}\text{Cl}_4\text{O}_8$ : C 44.21, H 3.51; Found: C 44.23, H 3.53.

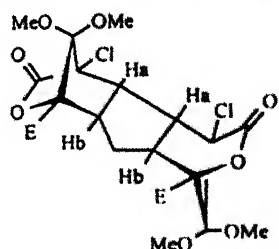
**Anti oxa-bridged derivative 175:** Yield: 58%; colorless crystals (EtOAc), mp 127 °C;  $^1\text{H}$  NMR  $\delta$  3.58 (s, 6H,  $\text{CO}_2\text{Me}$ ), 3.54 (s, 6H,  $\text{CO}_2\text{Me}$ ), 3.46 (dd, 2H ( $\text{H}_b$ ),  $J$  = 14.2, 6.8 Hz), 3.38 (s, 6H, OMe), 3.29 (s, 6H, OMe), 3.04 (d, 2H ( $\text{H}_a$ ),  $J$  = 6.6 Hz), 1.72 (t, 2H ( $\text{H}_c$ ),  $J$  = 7.2 Hz);  $^{13}\text{C}$  NMR  $\delta$  166.4 (2C, -O-C=O), 166.2 (2C, -O-C=O), 113.0 (2C), 92.7 (2C), 90.9 (2C), 52.9 (2C, OMe), 52.6 (2C, OMe), 52.5 (2C), 51.9 (2C), 51.8 (2C), 51.7 (2C), 26.3; IR (KBr)



2900, 1720, 1440, 1380  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{23}\text{H}_{30}\text{O}_{14}$ : C 52.08, H 5.70; Found: C 52.10, H 5.72.

**$\text{C}_2$ -Symmetric pentacyclic bis-lactone 181:** To a stirred solution of diketone (100 mg, 0.194 mmol) in THF (2 ml) and methanol (2 ml) was

added 30%  $\text{H}_2\text{O}_2$  (0.22 ml) followed by slow addition of 6N  $\text{NaOH}$  solution (0.1ml). After stirring at room temperature ( $\sim 20^\circ\text{C}$ ) for 1 h. 5%  $\text{HCl}$  (2 ml) was added and extracted with ethyl acetate (3 $\times$ 5 ml). The combined ethyl acetate layer was washed once with brine and dried over  $\text{Na}_2\text{SO}_4$ . The crude carboxylic acid obtained after concentration of ethyl acetate layer was treated with excess diazomethane in ether:methanol (1:1) at  $0^\circ\text{C}$ . After quenching excess diazomethane

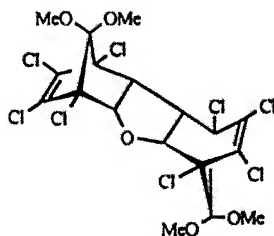


with acetic acid, the solution was concentrated and silica gel column chromatography afforded the pure product. Yield: 80%; colorless crystals ( $\text{EtOAc}$ ). mp  $216\text{--}218^\circ\text{C}$ .  $^1\text{H}$  NMR  $\delta$  3.83 (s, 6H,  $\text{CO}_2\text{Me}$ ), 3.70 (dd, 2H

( $\text{H}_b$ ),  $J = 16.7, 8.7$  Hz), 3.58 (s, 6H, OMe), 3.69 (s, 6H, OMe), 2.99 (d, 2H ( $\text{H}_b$ ),  $J = 11.7$ ), 1.92 (t, 2H ( $\text{CH}_2$ ),  $J = 8.1$  Hz);  $^{13}\text{C}$  NMR  $\delta$  167.2 (2C,  $-\text{O}-\text{C}=\text{O}$ ), 165.2 (2C,  $-\text{O}-\text{C}=\text{O}$ ), 111.0 (2C), 86.3 (2C), 75.0 (2C), 53.4 (2C, OMe), 51.9 (2C, OMe), 51.8 (2C), 50.5 (2C), 49.7 (2C), 22.4. IR (KBr) 2900, 1800, 1740, 1440, 1320, 1280  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{21}\text{H}_{24}\text{O}_{12}\text{Cl}_2$ : C 46.77, H 4.49; Found: C 46.79, H 4.52.

**Bis adduct 182:** The tetrachloro cyclopentadiene **5** (4 mmol, 1.056 g) was treated with 2 g of furan in 0.5 ml of benzene in a sealed tube for 48 h to furnish 846 mg of *endo,anti,endo* adduct **182**. The reaction mixture was a solid; which was washed with hexane to furnish the pure

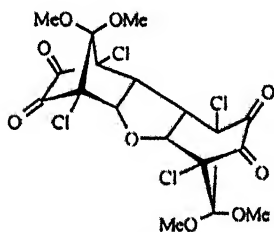
product. Yield: 71% (Lit. 55%); colorless solid, mp 222-224 °C (Lit.<sup>59</sup>



243 °C); <sup>1</sup>H NMR δ 4.70 (d, 2H, *J* = 6.3 Hz), 3.56 (s, 6H, OMe), 3.52 (s, 6H, OMe), 3.10 (d, 2H, *J* = 6.3 Hz); <sup>13</sup>C NMR δ 130.1 (2C), 128.4(2C), 114.1 (2C), 93.7 (2C), 78.0 (2C), 76.0 (2C), 53.1 (2C), 52.6 (2C), 51.7 (2C); IR (KBr) 2900, 1600, 1420,

1330, 1280, 1260 cm<sup>-1</sup>; Anal. calcd. for C<sub>18</sub>H<sub>16</sub>Cl<sub>3</sub>O<sub>5</sub>: C 36.28, H 2.71; Found: C 36.25, H 2.73.

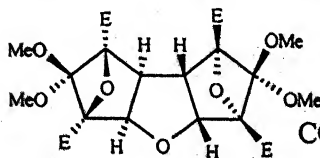
**Bis α-diketone 182:** Yield: 96%; yellow solid, mp 245-247 °C (dec);



<sup>1</sup>H NMR δ 4.61 (d, 2H, *J* = 8.1 Hz), 3.68 (s, 6H, OMe), 3.52 (s, 6H, OMe), 3.21 (d, 2H, *J* = 8.1 Hz); <sup>13</sup>C NMR δ 187.3 (2C, -C=O), 183.5 (2C, -C=O), 104.5 (2C), 88.9 (2C), 78.9 (2C), 76.8 (2C), 52.4 (2C), 49.9 (2C);

IR (KBr) 2900, 1760, 1440, 1200 cm<sup>-1</sup>; Anal. calcd. for C<sub>18</sub>H<sub>16</sub>Cl<sub>4</sub>O<sub>7</sub>: C 44.47, H 3.32; Found: C 44.51, H 3.34.

**Anti oxa-bridge derivative 176:** Yield: 57%; colorless crystals

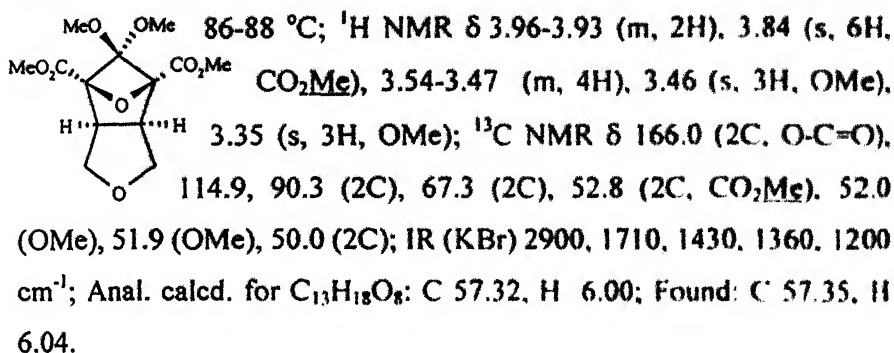


(EtOAC), mp 175 °C; <sup>1</sup>H NMR δ 5.28 (*J* = 5.1 Hz), 3.87 (s, 6H, CO<sub>2</sub>Me), 3.84 (s, 6H, CO<sub>2</sub>Me), 3.37 (s, 6H, OMe), 3.30 (s, 6H, OMe), 3.19 (d, 2H, *J* = 5.1 Hz); <sup>13</sup>C NMR δ 165.4 (2C, -O-C=O), 164.9 (2C, -O-C=O), 113.6 (2C), 91.7 (2C), 90.9 (2C), 89.7 (2C), 52.8 (2C,



OMe), 52.7 (2C, OMe), 51.9 (4C, OMe), 50.1 (2C); IR (KBr) 2900, 1720, 1420, 1280  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{22}\text{H}_{28}\text{O}_{15}$ : C 49.63, H 5.30; Found: C 49.66, H 5.32.

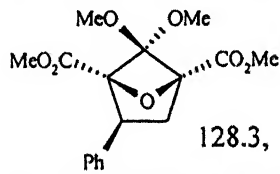
**Tricyclic oxa-bridge derivative 163t:** Yield: 53%; colorless solid, mp



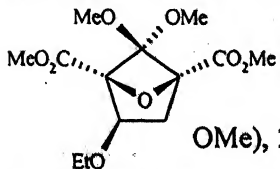
**One-pot synthesis of oxa-bridged compounds 163a,b:** The same procedure described above was performed with monosubstituted diketones **2a,b** and **61**. To a stirred solution of diketone (0.5 mmol) in methanol (4 ml) was added 30%  $\text{H}_2\text{O}_2$  (0.38 ml) followed by slow addition of 6N NaOH solution (0.15 ml). After stirring at room temperature ( $\sim 20^\circ\text{C}$ ) for 3 h, a solution of NaOH (15 mmol) in  $\text{H}_2\text{O}$  (1.5 ml) was added. The mixture was refluxed for 31 h, cooled and 10% HCl (10 ml) was added and extracted with ethyl acetate ( $4 \times 5$  ml). The combined ethyl acetate layer was washed once with brine and dried over  $\text{Na}_2\text{SO}_4$ . The crude carboxylic acid obtained after concentration of ethyl acetate layer was treated with excess diazomethane in

ether:methanol (1:1) at 0 °C. After quenching excess diazomethane with acetic acid, the solution was concentrated and silica gel column chromatography (50% ethyl acetate-hexane) afforded the pure product in specified yields (Scheme 15).

**Dimethyl 6,6-Dimethoxy-2-phenyl-5-oxa-bicyclo[2.1.1]hexane-1,4-dicarboxylate 163a:** Yield: 69%, colorless solid, mp 98-100 °C,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.40-7.20 (m, 5H), 3.93 (dd, 1H,  $J$  = 8.5, 3.9 Hz), 3.87 (s, 3H, OMe), 3.56 (s, 3H, OMe), 3.54 (s, 3H, OMe), 3.37 (s, 3H, OMe), 2.98 (dd, 1H,  $J$  = 11.7, 8.5 Hz), 2.20 (dd, 1H,  $J$  = 11.7, 4.2 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  166.9 (O-C=O), 166.1 (O-C=O), 139.0, 128.7, 128.3, 127.3, 111.1, 93.4, 88.6, 52.6, 52.2, 52.0, 51.7, 47.4, 39.9; IR (Neat) 2946, 1728, 1497, 1458, 1454, 1371, 1299, 1167, 1095, 797  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{17}\text{H}_{20}\text{O}_7$ : C 60.71, H 5.99; Found: C 60.64, H 6.03.



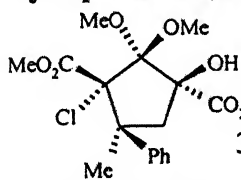
**Dimethyl 2-Ethoxy-6,6-dimethoxy-5-oxa-bicyclo[2.1.1]hexane-1,4-dicarboxylate 163b:** Yield: 63%; colorless viscous liquid,  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.55 (dd, 1H,  $J$  = 6.6, 1.2 Hz), 3.86 (s, 3H, OMe), 3.83 (s, 3H, OMe), 3.60-3.52 (m, 1H), 3.51-3.46 (m, 1H), 3.43 (s, 3H, OMe), 3.33 (s, 3H, OMe), 2.77 (dd, 1H,  $J$  = 11.7, 6.6 Hz), 1.94 (dd, 1H,  $J$  = 12.0, 1.2 Hz), 1.17 (t,  $J$  = 6.8 Hz);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$



166.4 (O-C=O), 166.1 (O-C=O), 111.3, 91.7, 88.7, 80.2, 65.6, 52.52, 52.48, 51.9, 51.6, 39.4, 15.1. IR (Neat) 2952, 1735, 1436, 1404, 1014, 73.3  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{13}\text{H}_{20}\text{O}_8$ : C 51.31, H 6.62; Found: C, 51.53, H, 6.54.

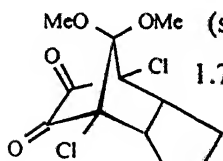
**Dimethyl 3-Chloro-1-hydroxy-2,2-dimethoxy-4-methyl-4-phenyl-cyclopentane-1,3-dicarboxylate 187:** Yield: 61%, colorless solid, mp

89-90 °C,  $^1\text{H}$  NMR  $\delta$  7.37-7.10 (m, 5H), 4.44 (s, D<sub>2</sub>O exchangeable), 3.73 (s, 3H, OMe), 3.56 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.37 (d, 1H,  $J = 14.4$  Hz), 3.31 (s, 3H, OMe), 2.85 (d, 1H,  $J = 14.4$  Hz), 1.57 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  171.8 (O-C=O), 171.5 (O-C=O), 145.4, 128.4, 128.1, 126.6, 125.5, 110.7, 88.8, 85.1, 54.0, 53.41, 53.37, 52.6, 49.8, 49.3, 28.8; IR (KBr) 3400, 2950, 1700, 1600, 1580, 1420, 1380  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{18}\text{H}_{22}\text{O}_7$ : C 61.71, H 6.33; Found: C 61.80, H 6.51.

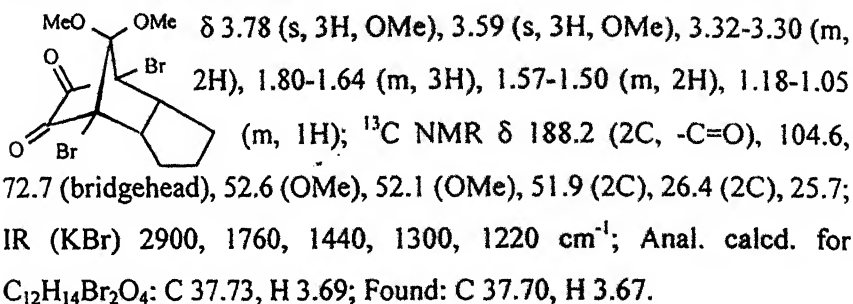


**Diketone 1i:** Yield: 98%; yellow solid, mp 88-89 °C;  $^1\text{H}$  NMR  $\delta$  3.74

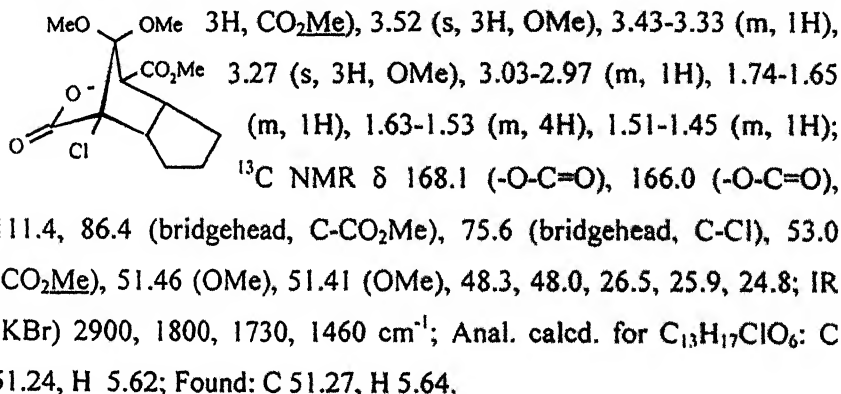
(s, 3H, OMe), 3.54 (s, 3H, OMe), 3.25-3.22 (m, 2H), 1.75-1.68 (m, 3H), 1.58-1.53 (m, 2H), 1.16-1.08 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  189.0 (2C, -C=O), 104.3, 80.1 (bridgehead), 52.5 (OMe), 52.1 (OMe), 50.6 (2C), 26.2, 26.1 (2C); IR (KBr) 2900, 1760, 1440, 1300, 1220  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{12}\text{H}_{14}\text{Cl}_2\text{O}_4$ : C 49.17, H 4.81; Found: C 49.20, H 4.83.



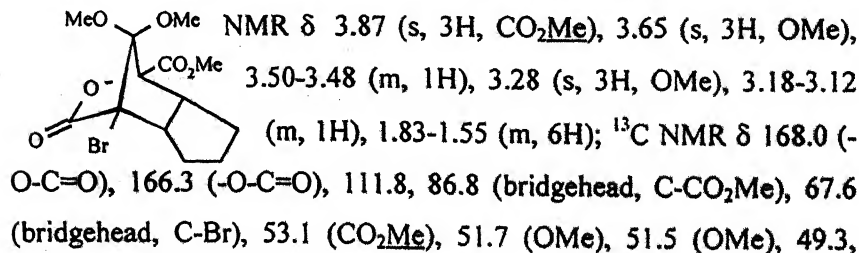
**Diketone 2i:** Yield: 92%; yellow solid, mp 129-130 °C;  $^1\text{H}$  NMR



**Tricyclic lactone 51i:** Yield: 95%; colorless solid,  $^1\text{H}$  NMR  $\delta$  3.77 (s,

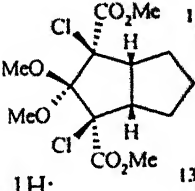


**Tricyclic lactone 52i:** Yield: 98%; colorless solid, mp 120-122 °C;  $^1\text{H}$



49.0, 26.5, 26.4, 24.9; IR (KBr) 2900, 1800, 1730, 1460  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{13}\text{H}_{17}\text{BrO}_6$ : C 44.72, H 4.91; Found: C 44.75, H 4.94.

**Diquinane derivative 50i:** Yield: 70%; colorless solid, mp 92-94  $^{\circ}\text{C}$ ;

  $^1\text{H}$  NMR  $\delta$  3.86 (s, 3H, OMe), 3.77 (s, 6H, OMe), 3.53 (s, 3H, OMe), 3.25-3.19 (m, 2H), 2.15-2.10 (m, 2H), 1.72-1.66 (m, 1H), 1.56-1.49 (m, 2H), 1.30-1.20 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  167.8 (2C,  $-\text{C}=\text{O}$ ), 110.9, 74.8 (2C), 56.3 (2C), 53.4 (2C,  $\text{CO}_2\text{Me}$ ), 52.5 (OMe), 52.3 (OMe), 33.2 (2C), 26.3; IR (KBr) 2900, 1720, 1440, 1200, 1000  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{14}\text{H}_{20}\text{Cl}_2\text{O}_6$ : C 47.34, H 5.67; Found: C 47.30, H 5.69.

**Diquinane derivative 188:** Yield: 62%; colorless solid, mp 138-140

$^{\circ}\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  3.86 (s, 3H, OMe), 3.77 (s, 6H, OMe), 3.55 (s, 3H, OMe), 3.30-3.24 (m, 2H), 2.17-2.10 (m, 2H), 1.74-1.59 (m, 1H), 1.25-1.17 (m, 2H), 0.94 (d, 1H,  $J=6.4$  Hz, Me), 0.98-0.92 (m, 2H, merged with Me doublet);  $^{13}\text{C}$  NMR  $\delta$  167.2 (2C,  $\text{O}-\text{C}=\text{O}$ ), 110.9, 74.8 (2C), 56.4 (2C), 53.4 (2C,  $\text{CO}_2\text{Me}$ ), 52.6 (OMe), 52.3 (OMe), 41.4 (2C), 34.4, 18.3 (Me); IR (KBr) 2900, 1740, 1430, 1220, 1060  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{15}\text{H}_{22}\text{Cl}_2\text{O}_6$ : C 48.79, H 6.01, Found: C 48.81, H 6.04.

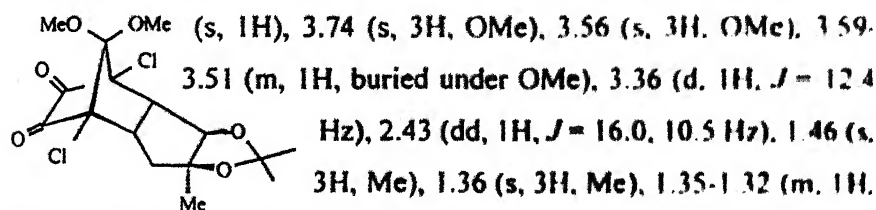
**Tetrachloro derivative 189:** Yield: 57%; colorless solid, mp 128-130 °C;  $^1\text{H}$  NMR  $\delta$  3.59 (s, 3H, OMe), 3.55 (s, 3H, OMe), 3.47 (d, 1H,  $J$  = 7.6 Hz), 3.37-3.30 (m, 1H), 3.03 (dd, 1H,  $J$  = 10.0, 7.3 Hz), 2.28 (br s, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 2.00 (dd, 1H,  $J$  = 14.0, 8.3 Hz), 1.24 (s, 3H, Me), 1.12 (dd, 1H,  $J$  = 14.02, 10.0 Hz);  $^{13}\text{C}$  NMR  $\delta$  130.7, 129.4, 115.5, 80.9, 77.5, 77.4, 76.8, 59.1, 52.5 (OMe), 51.7 (OMe), 50.8, 35.9, 24.3; IR (KBr) 3300, 2900, 1600, 1440, 1370, 1250  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{13}\text{H}_{16}\text{Cl}_4\text{O}_4$ : C 41.30, H 4.27; Found: C 42.33, H 4.29.

**Keto aldehyde 190:** Yield: 11%; colorless solid, mp 98-100 °C;  $^1\text{H}$  NMR  $\delta$  9.76 (s, 1H, CHO), 3.60 (s, 3H, OMe), 3.57 (s, 3H, OMe), 3.30 (ddd, 1H,  $J$  = 11.5, 4.2, 3.2 Hz), 2.99 (dd, 1H,  $J$  = 17.4, 2.8 Hz), 2.19 (s, 3H, Me), 2.15-2.13 (m, 1H), 2.10-2.08 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  206.1 ( $-\text{C}=\text{O}$ ), 196.9 (CHO), 130.7, 130.2, 111.5, 77.3, 76.5, 52.9, 52.8, 51.6, 44.5, 43.0, 29.9. IR (KBr) 2850, 1700, 1600, 1400, 1360, 1240  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{13}\text{H}_{14}\text{Cl}_4\text{O}_4$ : C 41.52, H 3.75; Found: C 41.55, H 3.78.

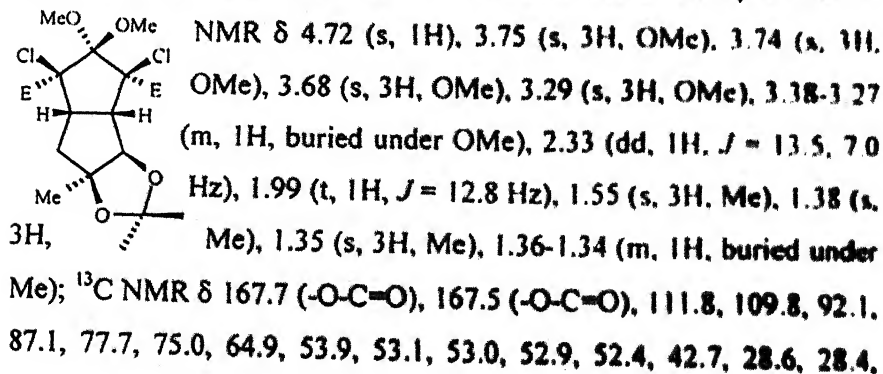
**Acetonide 191:** Yield: 80%; colorless solid, mp 68-70 °C;  $^1\text{H}$  NMR  $\delta$  4.18 (s, 1H), 3.59 (s, 3H, OMe), 3.53 (s, 3H, OMe), 3.50-3.43 (m, 1H), 3.23 (dd, 1H,  $J$  = 9.6, 2.0 Hz), 2.31 (dd, 1H,  $J$  = 15.8, 10.0 Hz), 1.60 (dd, 1H,  $J$  = 15.8, 5.9 Hz), 1.46 (s, 3H, Me), 1.38 (s, 3H, Me).

Me), 1.34 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  130.6, 129.3, 114.9, 111.5, 93.4, 86.3, 78.1, 76.5, 62.5, 53.8, 52.5, 51.7, 39.2, 28.7, 28.2, 25.8. IR (KBr) 2850, 1600, 1440, 1260  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{16}\text{H}_{20}\text{Cl}_4\text{O}_4$ : C 45.12, H 4.66; Found: C 45.37, H 4.58.

**Diketone 192:** Yield: 91%; colorless solid, mp 80  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  4.01

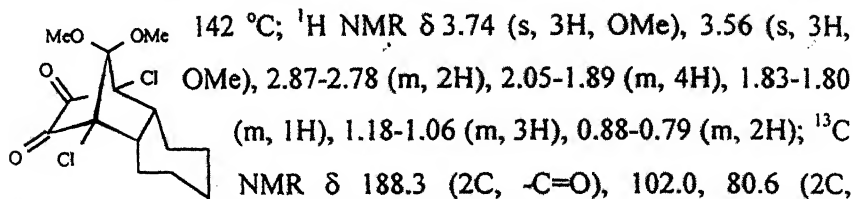


**Diquinane derivative 193:** Yield: 89%; colorless solid, mp 89  $^{\circ}\text{C}$ ;  $^1\text{H}$



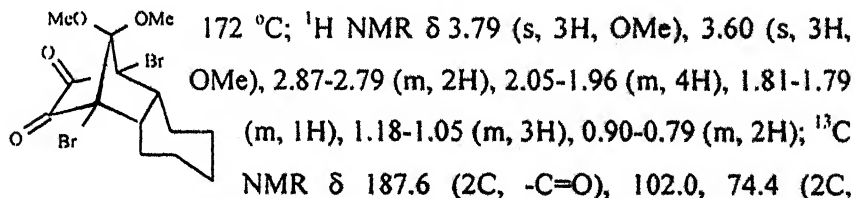
24.7; IR (KBr) 2900, 1720, 1420, 1360, 1260  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{18}\text{H}_{26}\text{Cl}_2\text{O}_8$ : C 48.99, H 5.94; Found: C 48.95, H 5.89.

**Diketone 1k:** Yield: 97%; yellow crystals ( $\text{CH}_2\text{Cl}_2$ -hexane), mp 140-



IR (KBr) 2850, 1780, 1430, 1360, 1340  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{14}\text{H}_{18}\text{Cl}_2\text{O}_4$ : C 52.35, H 5.65, Found: C 52.40, H 5.67.

**Diketone 2k:** Yield: 91%; yellow crystals ( $\text{CH}_2\text{Cl}_2$ -hexane), mp 170-

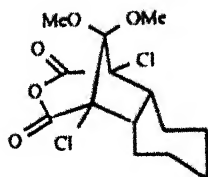


IR (KBr) 2900, 1780, 1440, 1300, 1280, 1200  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{14}\text{H}_{18}\text{Br}_2\text{O}_4$ : C 41.00, H 4.42, Found: C 41.04, H 4.40.

**1,9-Dichloro-13,13-dimethoxy-11-oxa-tricyclo[7.3.1.0<sup>2,8</sup>]tridecane-10,12-dione 19a:** Yield: 77 %; colorless solid, mp 120 °C;  $^1\text{H}$  NMR  $\delta$  3.80 (s, 3H, OMe), 3.58 (s, 3H, OMe), 2.88-2.84 (m, 2H), 2.05-1.96

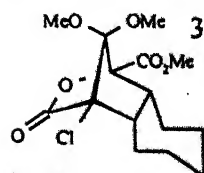


(m, 4H), 1.86-1.83 (m, 1H), 1.21-1.10 (m, 5H);  $^{13}\text{C}$  NMR  $\delta$  161.6 (2C, O-C=O), 102.5, 79.9 (2C, bridgehead), 53.5 (OMe), 53.3 (OMe), 50.5 (2C), 30.5, 28.8 (2C), 28.4 (2C); IR (KBr) 2850, 1820, 1760, 1440  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{14}\text{H}_{17}\text{Cl}_2\text{O}_4$ : C 49.87, H 5.38, Found: C 49.91, H 5.34



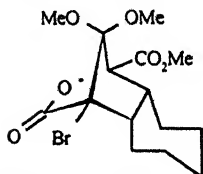
**1,3-Dichloro-2,2-dimethoxy-decahydro-azulene-1,3-dicarboxylic acid dimethyl ester 50k:** Yield: 71%;  $^1\text{H}$  NMR  $\delta$  3.80 (s, 3H, OMe), 3.73 (s, 6H,  $\text{CO}_2\text{Me}$ ), 3.60 (s, 3H, OMe), 2.93-2.91 (m, 2H), 1.91-1.80 (m, 5H), 1.30-1.19 (m, 3H), 1.12-1.01 (m, 2H);  $^{13}\text{C}$  NMR  $\delta$  167.9 (2C, O-C=O), 107.3, 78.5 (2C, C<sub>3</sub>), 54.0 (2C,  $\text{CO}_2\text{Me}$ ), 53.8 (OMe), 53.5 (OMe), 52.7 (2C), 31.1, 29.7 (2C), 25.6 (2C); IR (KBr) 2850, 1700, 1430, 1360, 1340  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{16}\text{H}_{24}\text{Cl}_2\text{O}_6$ : C 50.14, H 6.31, Found: C 50.19, H 6.35.

**Tricyclic lactone 51k:** Yield: 92%; colorless solid, mp 124  $^\circ\text{C}$ .  $^1\text{H}$  NMR  $\delta$  3.86 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.63 (s, 3H, OMe), 3.37 (s, 3H, OMe), 3.15 (ddd, 1H,  $J = 12.7, 10.9, 3.8$  Hz), 2.66 (m, 1H), 2.02-1.95 (m, 3H), 1.83-1.82 (m, 1H), 1.53-1.39 (m, 2H), 1.22-1.01 (m, 4H);  $^{13}\text{C}$  NMR  $\delta$  167.7 (-O-C=O), 166.1 (-O-C=O), 108.4, 87.8 (bridgehead, C-CO<sub>2</sub>Me), 76.8 (bridgehead, C-Cl), 53.1 ( $\text{CO}_2\text{Me}$ ), 51.61 (OMe), 51.55



(OMe), 47.6, 46.2, 30.6, 28.7 (2C), 25.4, 24.7; IR (KBr) 2900, 1800, 1740, 1420, 1300, 1200  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{15}\text{H}_{21}\text{ClO}_6$ : C 54.14, H 6.36; Found: C 54.19, H 6.39.

**Tricyclic lactone 52k:** Yield: 97%; colorless solid, mp 138-140  $^{\circ}\text{C}$ ;  $^1\text{H}$  NMR  $\delta$  3.86 (s, 3H,  $\text{CO}_2\text{Me}$ ), 3.67 (s, 3H, OMe), 3.37 (s, 3H, OMe), 3.16 (ddd, 1H,  $J = 12.3, 10.6, 3.5$  Hz), 2.68 (dt, 1H,  $J = 11.8, 2.4$  Hz), 2.02-1.95 (m, 3H), 1.83-1.81 (m, 1H), 1.57-1.40 (m, 2H), 1.25-1.04 (m, 4H);  $^{13}\text{C}$  NMR  $\delta$  167.5 (-O-C=O), 166.2 (-O-C=O), 108.4, 88.2 (bridgehead, C- $\text{CO}_2\text{Me}$ ), 69.7 (bridgehead, C-Br), 53.1 ( $\text{CO}_2\text{Me}$ ), 51.61 (OMe), 51.58 (OMe), 48.3, 46.8, 30.5, 28.8 (2C), 26.1, 24.7; IR (KBr) 2900, 1800, 1740, 1430, 1300, 1190  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{15}\text{H}_{21}\text{BrO}_6$ : C 47.76, H 5.61; Found: C 47.80, H 5.64.



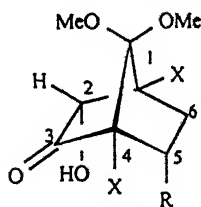
## Chapter 3A

### Regio- and Diastereoselective Reduction of Non-enolizable $\alpha$ -Diketones to Acyloins Mediated by Indium Metal

**General procedure for the indium mediated reduction of  $\alpha$ -diketones:** A mixture of  $\alpha$ -diketone (0.3 mmol), indium metal (0.6 mmol, cut into small pieces) and  $\text{NH}_4\text{Cl}$  (0.9 mmol) in  $\text{MeOH}$  (4ml) and water (1ml) was refluxed for the specified time (Table 1, 2 and Scheme 1). After completion of the reaction, as monitored by tlc, the reaction mixture was quenched with 3 ml of 5%  $\text{HCl}$  and extracted with ethyl acetate. Combined organic layer was washed once with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Concentration followed by silica gel column chromatography gave the acyloins in the specified yields.

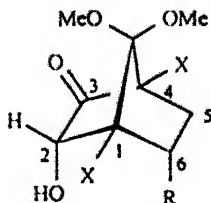
**General procedure for the cleavage of acyloins:** To a stirred solution of the acyloins (0.2 mmol) in  $\text{MeOH}$  (3ml) and benzene (1 ml) was added  $\text{Pb}(\text{OAc})_4$  (0.5 mmol) in portions over a period of 15 min. at room temperature. After stirring for the required time (monitored by tlc, Scheme 2), 3 ml of water was added and reaction mixture extracted with ethyl acetate. Combined organic layer was washed with water, once with dil.  $\text{NaHCO}_3$  solution, once with brine and dried over anhydrous  $\text{Na}_2\text{SO}_4$ . Concentration followed by silica gel chromatography of the crude yielded the pure cyclopentane carboxaldehydes.

## Spectral Data For Monosubstituted Acyloins:



X=Cl, 196a-f,u

X=Br, 198a-d,u

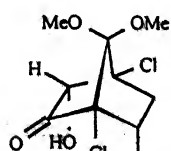


X=Cl, 197b-f, u

X=Br, 199a-d,u

The carbinol hydrogen is assigned as  $C_2$  in all the mono and disubstituted acyloins to observe the long range, W-Coupling range (0.7-2.4 Hz) between the carbinol *exo*-hydrogen at  $C_2$  with respect to the *exo* hydrogen on the carbon  $C_6$  ( $C_2$  and  $C_6$  are in 1,3- relation) and also to compare the of  $^1\text{H}$  NMR (400 MHz) values of *exo* and *endo* protons on the carbon  $C_6$  and  $C_5$  with those of the parent  $\alpha$ -diketone (the comparison table (Table 2) is given under results and discussion of this chapter) to assign the regioselectivity for the formation of major isomer.

**Acyloin 196a:** Yield 100%, colorless solid, mp 106–108 °C,  $^1\text{H}$  NMR  $\delta$  7.29–7.26 (m, 5H, aromatic), 4.56 (br s, 1H), 3.79 (s, 3H, OMe), 3.74

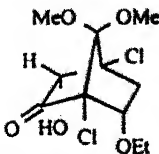
(dd, 1H,  $J=12.2, 5.6$  Hz,  $C(5)H_{\text{exo}}$ ), 3.73 (br s, 1H, $\text{D}_2\text{O}$  exchangeable, OH), 3.65 (s, 3H, OMe), 2.92 (dd,1H,  $J=13.1, 5.6$  Hz,  $C(6)H_{\text{endo}}$ ), 2.67 (dt, 1H,  $J=13.1, 1.9$ Hz,  $C(6)H_{\text{exo}}$ );  $^{13}\text{C}$  NMR  $\delta$  200.3 (C=O), 134.9, 129.4,

128.2, 127.9, 103.3, 82.0, 78.3 (carbinol C), 69.7, 51.8 (OMe), 51.7

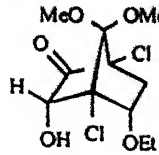
(OMe), 48.7, 34.4; IR (KBr) 3500, 2950, 1770, 1100  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{15}\text{H}_{16}\text{Cl}_2\text{O}_4$ : C 54.40, H 4.87; Found C 54.41, H 4.90.

**Acyloin 196b, 197b:** Yield 100%, mixture of regioisomers (71:29).

**Major isomer 196b:** colorless solid, mp 102-104  $^{\circ}\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  4.46

 (dd, 1H,  $J=6.2, 1.6$  Hz, carbinol H), 4.13(dd, 1H,  $J=9.5, 2.2$  Hz, C(5) $\text{H}_{\text{exo}}$ ), 3.68 (s, 3H, OMe), 3.67 (dq, 1H, merged with OMe), 3.59 (s, 3H, OMe), 3.52 (dq, 1H,  $J=9.0, 7.1$  Hz,  $-\text{O}-\text{CH}_2$ ), 2.98 (d, 1H,  $J=6.2$  Hz,  $\text{D}_2\text{O}$  exchangeable, OH), 2.63 (ddd,  $J=13.1, 9.5, 1.6$  z, C(6) $\text{H}_{\text{exo}}$ ), 2.48 (dd,  $J=13.1, 2.2$  Hz, C(6) $\text{H}_{\text{endo}}$ ), 1.13 (t, 3H,  $J=7.1$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  197.5 (C=O), 103.1 ( $\text{C}_7$ ), 80.9, 80.1, 79.0, 69.4, 66.7, 51.9, 51.8, 36.9, 15.1; IR(KBr) 3400, 2900, 1780, 1440  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{11}\text{H}_{16}\text{Cl}_2\text{O}_5$ : C 44.17, H 5.39; Found: C, 43.87, H 5.10.

**Minor isomer 197b:** colorless solid, mp 113-115 $^{\circ}\text{C}$   $^1\text{H}$  NMR  $\delta$  4.70 (d, 1H,  $J=11.0$  Hz, carbinol H), 4.45 (dd, 1H,  $J=11.0, 2.2$  Hz,  $-\text{O}-\text{CH}_2$ ),

 4.39 (td, 1H,  $J=9.8, 2.2$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 3.66 (s, 3H, OMe), 3.64 (m, 1H,  $-\text{O}-\text{CH}_2$ ), 3.62 (s, 3H, OMe), 2.77 (dd, 1H,  $J=13.3, 9.6$  Hz, C(5) $\text{H}_{\text{exo}}$ ), 1.96 (dd, 1H,  $J=13.3, 2.7$  Hz, C(5) $\text{H}_{\text{endo}}$ ), 1.23 (t, 3H,  $J=7.0$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  201.1 (C=O), 102.5 ( $\text{C}_7$ ), 83.4, 81.1, 74.3, 70.2, 67.7, 51.8, 51.7, 40.4, 15.1; IR(KBr) 3500, 2950, 1720, 1380  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{11}\text{H}_{16}\text{Cl}_2\text{O}_5$ : C 44.17, H 5.39; Found: C 44.23, H 5.42.

**Acyloin 196c,197c:** Yield 84%, inseparable mixture of regioisomers (93:7), colorless solid, mp 86-87 °C; IR (KBr) 3300, 2900, 1760, 1690, 1200  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{12}\text{H}_{16}\text{Cl}_2\text{O}_6$ : C 44.06, H 4.92; Found C 44.20, H 5.18.

**Major isomer 196c:**  $^1\text{H}$  NMR  $\delta$  4.43 (dd, 1H,  $J=5.1, 1.7$  Hz, carbinol H), 4.10 (dd, 1H,  $J=11.8, 4.6$  Hz), 3.96 (dd, 1H,  $J=11.8, 6.6$  Hz), 3.70

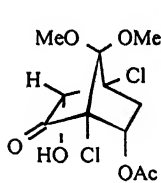
(s, 3H, OMe), 3.62 (s, 3H, OMe), 3.43 (d, 1H,  $J=5.1$  Hz,  $\text{D}_2\text{O}$  exchangeable, OH), 2.88-2.81 (m, 1H,  $\text{C}(5)\text{H}_{\text{exo}}$ ), 2.46 (dd, 1H,  $J=12.8, 5.6$  Hz,  $\text{C}(6)\text{H}_{\text{endo}}$ ), 2.40 (dt, 1H,  $J=12.8, 1.7$  Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 2.03 (s, 3H,  $\text{OCOMe}$ );  $^{13}\text{C}$  NMR  $\delta$  200.1 ( $\text{C}=\text{O}$ ), 170.6 ( $\text{OC}=\text{O}$ ), 102.9, 78.4, 78.3, 69.6, 61.6, 51.8, 51.6, 41.9, 31.2, 20.6.

**Minor isomer 197c:**  $^1\text{H}$  NMR  $\delta$  4.62 (br s, 1H, carbinol H), 4.47 (dd, 1H,  $J=11.6, 3.4$  Hz), 4.37 (dd, 1H,  $J=11.6, 9.7$  Hz), 3.70 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.04-2.96 (m, 1H, one of  $J$  is 1.7 Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 2.61 (t, 1H,  $J=13.1$  Hz,  $\text{C}(5)\text{H}_{\text{exo}}$ ), 2.06 (s, 3H,  $\text{OAc}$ ), 1.84 (dd, 1H,  $J=13.1, 5.6$  Hz,  $\text{C}(5)\text{H}_{\text{endo}}$ );  $^{13}\text{C}$  NMR  $\delta$  201.6 ( $\text{C}=\text{O}$ ), 171.4 ( $\text{O}-\text{C}=\text{O}$ ), 102.7, 79.9, 74.7, 72.3, 64.7, 51.8 (OMe), 51.7 (OMe), 42.9, 37.6, 20.9.

For both the isomers 196c, 197c  $J=1.7$  Hz for  $\text{C}(2)\text{H}_{\text{exo}}$  and  $\text{C}(6)\text{H}_{\text{endo}}$  was confirmed by decoupling experiments.

**Acyloin 196d,197d:** Yield 90%, mixture of regioisomers (70:30) in THF-H<sub>2</sub>O.

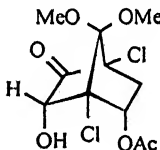
**Major isomer 196d:** colorless solid, mp 97-99 °C, <sup>1</sup>H NMR δ 5.35 (dd, 1H, *J*=10.2, 3.2 Hz, C(5)H<sub>exo</sub>), 4.52 (dd, 1H, *J*=4.6, 2.2 Hz, carbinol H), 3.71 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.48 (d, 1H, *J*=4.9 Hz, D<sub>2</sub>O exchangeable, OH), 2.76 (ddd, 1H, *J*=13.6, 10.2, 2.2 Hz, C(6)H<sub>exo</sub>),



2.48 (dd, 1H, *J*=13.6, 3.2 Hz, C(6)H<sub>endo</sub>), 2.06 (s, 3H, OCOMe); <sup>13</sup>C NMR δ 197.5 (C=O), 170.1 (O-C=O), 102.7, 78.7, 78.3, 73.3, 69.1, 51.9, 51.8, 35.9, 20.6; IR (KBr) 3300, 2900, 1760, 1700, 1360, 1200 cm<sup>-1</sup>; Anal.

Calcd. for C<sub>11</sub>H<sub>14</sub>Cl<sub>2</sub>O<sub>6</sub>: C 42.19, H 4.51; Found: C 41.93, H 4.89.

**Minor isomer 197d:** (from the mixture) <sup>1</sup>H NMR δ 5.54 (ddd, 1H,

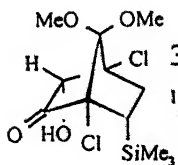


*J*=10.1, 3.2, 1.8 Hz, C(6)H<sub>exo</sub>), 4.61 (dd, 1H, *J*=1.8 Hz, carbinol H), 3.69 (s, 3H, OMe), 3.65 (s, 3H, OMe), 2.97 (dd, 1H, *J*=14.0, 10.1 Hz, C(5)H<sub>exo</sub>), 2.16 (s, 3H, OCOMe), 1.89 (dd, 1H, *J*=14.0, 3.2 Hz, C(5)H<sub>endo</sub>); <sup>13</sup>C NMR δ 200.5 (C=O), 169.3 (O-C=O), 102.6, 80.9, 76.9, 73.9, 70.2, 52.0, 51.8, 40.3, 20.8.

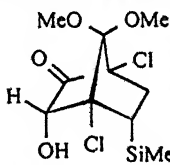
**Acyloin 196e, 197e:** Yield: 96%, mixture of regioisomers (81:19).

**Major isomer 196e:** colorless solid, mp 100-101 °C, <sup>1</sup>H NMR δ 4.37 (dd, 1H, *J*=4.2, 2.0 Hz, carbinol H), 3.67 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.03 (d, 1H, *J*=4.2 Hz, OH, D<sub>2</sub>O exchangeable), 2.38 (dd, 1H, *J*=12.3, 6.8 Hz, C(5)H<sub>exo</sub>), 2.25 (dt, 1H, *J*=12.5, 2.0 Hz, C(6)H<sub>exo</sub>), 1.95

(dd, 1H,  $J=12.9, 6.8$  Hz, C(6)H<sub>endo</sub>), 0.0 (s, 9H, SiMe<sub>3</sub>); <sup>13</sup>C NMR  $\delta$  201.9 (C=O), 103.0, 79.1, 78.2, 70.1, 51.7, 51.4, 31.2, 30.2, -1.96; IR (KBr) 3400, 2900, 1760, 1440, 1200 cm<sup>-1</sup>; Anal. Calcd for C<sub>12</sub>H<sub>20</sub>Cl<sub>2</sub>O<sub>4</sub>Si: C 44.04, H 6.16; Found C 43.97, H 6.20.

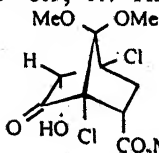


**Minor isomer 197e:** colorless solid, mp. 119-121 °C, <sup>1</sup>H NMR  $\delta$  4.57 (s, 1H, carbinol H), 3.72 (s, 3H, OMe), 3.61 (s, 3H, OMe), 2.89 (d, 1H,  $J=4.2$  Hz, OH, D<sub>2</sub>O exchangeable), 2.47 (t, 1H,  $J=12.7$  Hz, C(5)H<sub>exo</sub>), 2.03 (ddd, 1H,  $J=13.1, 6.1, 2.0$  Hz, C(6)H<sub>exo</sub>), 1.75 (dd, 1H,  $J=12.1, 6.2$  Hz, C(6)H<sub>endo</sub>), 0.08 (s, 9H, SiMe<sub>3</sub>); <sup>13</sup>C NMR  $\delta$  203.1 (C=O), 103.8, 80.3 (carbinol C), 76.0, 75.0, 54.0, 52.3, 34.9, 30.8, 0.00; IR (KBr) 3400, 2900, 1750, 1420, 970 cm<sup>-1</sup>; Anal. Calcd for C<sub>12</sub>H<sub>20</sub>Cl<sub>2</sub>O<sub>4</sub>Si: C 44.04, H 6.16; Found C, 44.18, H 6.02.



**Acylolin 196f,197f:** Yield 76%, mixture of regioisomers (65:35).

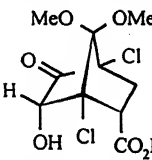
**Major isomer 196f:** colorless viscous liquid, <sup>1</sup>H NMR  $\delta$  4.43 (dd, 1H,  $J=8.9, 1.7$  Hz, carbinol H), 3.77 (br s, 1H, OH, D<sub>2</sub>O exchangeable), 3.75 (s, 3H, OMe), 3.72 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.41 (dd, 1H,  $J=11.5, 4.1$  Hz, C(5)H<sub>exo</sub>), 2.64 (dd, 1H,  $J=12.9, 4.1$  Hz, C(6)H<sub>exo</sub>), 2.55 (dt, 1H,  $J=12.9, 1.7$  Hz, C(6)H<sub>endo</sub>); <sup>13</sup>C NMR  $\delta$  198.6 (C=O), 173.3 (O-C=O), 103.1, 79.0 (2C), 69.4, 53.4 (OMe), 52.0 (OMe), 51.8 (OMe), 48.7, 32.0; IR





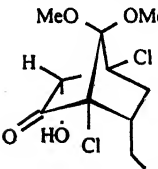
(KBr) 3300, 2900, 1760, 1700, 1370, 1200  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{O}_6$ : C 42.19, H 4.51; Found C 42.37, H 4.57.

**Minor isomer 197f:** colorless solid, mp 122-124  $^{\circ}\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  4.59

 (d, 1H,  $J=5.6$  Hz, carbinol H), 3.75 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.67 (d, 1H,  $J=6.1$  Hz, OH,  $\text{D}_2\text{O}$  exchangeable), 3.63 (s, 3H, OMe), 3.49 (dd, 1H,  $J=10.4, 6.7$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.56-2.48 (m, 2H);  $^{13}\text{C}$  NMR  $\delta$  200.3 (C=O), 172.0 (O-C=O), 103.1, 79.8, 73.9, 71.9, 52.8 (OMe), 51.9 (2C, OMe), 45.5, 34.2; IR (KBr) 3400, 2900, 1760, 1700, 1360, 1340  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{11}\text{H}_{14}\text{Cl}_2\text{O}_6$ : C 42.19, H 4.51; Found C 42.22, H 4.53.

**Acyloin 196u, 197u:** Yield 99%, inseparable mixture of regioisomers (80:20), colorless solid, mp 98-99  $^{\circ}\text{C}$ ; IR (KBr); 3300, 2900, 1760, 1380, 1180, 1040  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{11}\text{H}_{16}\text{Cl}_2\text{O}_5$ : C 44.17, H 5.39; Found C 43.98, H 5.12.

**Major isomer 196u:**  $^1\text{H}$  NMR  $\delta$  4.30 (dd, 1H,  $J=10.7, 1.2$  Hz, carbinol

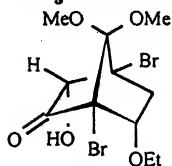
 H), 3.94 (d, 1H,  $J=10.7$  Hz,  $\text{D}_2\text{O}$  exchangeable, OH), 3.70 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.54 (dd, 1H,  $J=10.3, 3.5$  Hz), 3.38 (dd, 1H,  $J=10.3, 2.0$  Hz), 3.25 (s, 3H, OMe), 2.69 (m, 1H, C(5) $\text{H}_{\text{exo}}$ ), 2.43-2.36 (m, 2H, one of the  $J=1.4$  Hz);  $^{13}\text{C}$  NMR  $\delta$  199.7 (C=O), 102.9, 79.1 (carbinol C), 74.6, 70.3, 67.9, 58.8 (OMe), 51.9 (OMe), 51.7 (OMe), 44.6, 29.7.

**Minor isomer 197u:**  $^1\text{H}$  NMR  $\delta$  5.51 (d, 1H,  $J=11.7$  Hz,  $\text{D}_2\text{O}$  exchangeable, OH), 4.51 (qt, 1H,  $J=11.7, 0.7$  Hz, carbinol H), 3.88 (dd, 1H,  $J=10.7, 1.7$  Hz), 3.70 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.44 (s, 3H, OMe), 3.40-3.36 (m, 1H, buried under peaks of major isomer), 2.88 (tddd, 1H,  $J=12.1, 6.1, 4.6, 1.7$  Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 2.46 (dd, 1H,  $J=12.7, 1.4$  Hz,  $\text{C}(5)\text{H}_{\text{exo}}$ ), 2.06 (dd, 1H,  $J=12.7, 6.1$  Hz,  $\text{C}(5)\text{H}_{\text{endo}}$ );  $^{13}\text{C}$  NMR  $\delta$  202.0 ( $\text{C}=\text{O}$ ), 103.1, 79.5 (carbinol C), 78.9, 73.3, 67.2, 59.3, 51.7 (OMe), 51.6 (OMe), 43.3, 32.9.

**Acyloin 198a:** Yield 91%, colorless solid, mp 115-118  $^\circ\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  7.31-7.23 (m, 5H, aromatic), 4.58 (br s, 1H, carbinol H), 3.84 (s, 3H, OMe), 3.78 (dd, 1H,  $J=12.2, 5.9$  Hz,  $\text{C}(5)\text{H}_{\text{exo}}$ ), 3.71 (s, 3H, OMe), 3.34 (br s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.98 (dd, 1H,  $J=13.1, 5.6$  Hz,  $\text{C}(6)\text{H}_{\text{endo}}$ ), 2.76 (ddd, 1H,  $J=13.1, 12.2, 2.2$  Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ );  $^{13}\text{C}$  NMR  $\delta$  200.4 ( $\text{C}=\text{O}$ ), 135.3, 129.5, 128.1, 127.9, 103.5, 79.0 (carbinol C), 75.9, 61.6, 52.0 (OMe), 51.8 (OMe), 50.2, 36.4; IR (KBr) 3500, 2950, 1750, 1100  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{15}\text{H}_{16}\text{Br}_2\text{O}_4$ : C 42.89, H 3.84; Found C 42.78, H 3.92.

**Acyloin 198b, 199b:** Yield 83%, mixture of regioisomers (81:19).

**Major isomer 198b:** colorless solid, mp 100-102 °C;  $^1\text{H}$  NMR  $\delta$  4.49



(dd, 1H,  $J=5.8, 1.7$  Hz, carbinol H), 4.17 (dd, 1H,  $J=9.5,$

2.7 Hz, C(5) $\text{H}_{\text{exo}}$ ), 3.73 (s, 3H, OMe), 3.67 (qd, 1H,

$J=9.7, 7.1$  Hz), 3.64 (s, 3H, OMe), 3.54 (qd, 1H,  $J=9.7,$

7.1 Hz), 2.99 (d, 1H,  $J=6.1$  Hz,  $\text{D}_2\text{O}$  exchangeable, OH), 2.70 (ddd, 1H,

$J=13.2, 9.5, 2.0$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.54 (dd, 1H,  $J=13.2, 2.7$  Hz, C(6) $\text{H}_{\text{endo}}$ ),

1.14 (t, 3H,  $J=7.1$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  197.5 (C=O), 103.1, 81.3, 79.7,

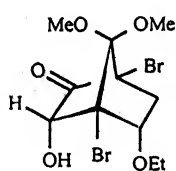
73.2, 66.8, 61.0, 52.0 (OMe), 51.9 (OMe), 38.5, 15.1 (Me); IR (KBr)

3300, 2850, 1760, 1200  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{11}\text{H}_{16}\text{O}_5\text{Br}_2$ : C 34.05, H

4.16; Found C 34.01, H 4.14.

**Minor isomer 199b:** colourless solid, mp 107-109 °C,  $^1\text{H}$  NMR  $\delta$  4.69

(d, 1H,  $J=11.0$  Hz, Carbinol H), 4.44-4.41 (m, 2H, one of the  $J=1.5$



Hz), 3.71 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.64 (q,

2H,  $J=7.1$  Hz), 2.80 (dd, 1H,  $J=13.4, 9.0$  Hz, C(5) $\text{H}_{\text{exo}}$ ),

2.01 (dd, 1H,  $J=13.4, 2.5$  Hz, C(5) $\text{H}_{\text{endo}}$ ), 1.23 (t, 3H,

$J=7.1$  Hz,  $\text{CH}_3$ );  $^{13}\text{C}$  NMR  $\delta$  201.2 (C=O), 102.5 ( $\text{C}_7$ ),

85.1 ( $\text{C}_2$ ), 81.8 ( $\text{C}_6$ ), 67.7, 66.5, 62.2, 51.9 (2C, OMe), 41.9, 15.1; IR

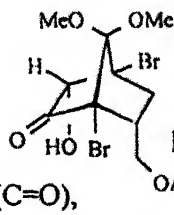
(KBr) 3250, 2800, 1760, 1200  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{11}\text{H}_{16}\text{O}_5\text{Br}_2$ : C

34.05, H 4.16; Found C 33.96, H 4.21.

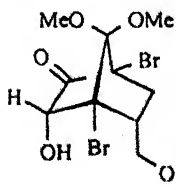
**Acyloin 198c, 199c:** Yield 68%, colorless viscous liquid, inseparable mixture of regioisomers (85:15). IR (KBr) 3400, 2950, 1740, 1200  $\text{cm}^{-1}$ ;

Anal. Calcd for  $\text{C}_{12}\text{H}_{16}\text{Br}_2\text{O}_6$ : C 34.64, H 3.88; Found C 34.57, H 3.76.

**Major isomer 198c:**  $^1\text{H}$  NMR  $\delta$  4.46 (br s, carbinol H), 4.13 (dd, 1H,  $J=11.7, 4.4$  Hz), 3.95 (dd, 1H,  $J=11.7, 6.6$  Hz), 3.75 (s, 3H, OMe), 3.67 (s, 3H, OMe), 2.88 (m, 1H, C(5) $\text{H}_{\text{exo}}$ ), 2.54 (dd, 1H,  $J=12.8, 5.4$  Hz, C(6) $\text{H}_{\text{endo}}$ ), 2.48 (dt, 1H,  $J=12.8, 2.0$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.03 (s, 3H, OCOMe);  $^{13}\text{C}$  NMR  $\delta$  200.2 (C=O), 170.7 (O-C=O), 102.9, 79.0, 71.4, 64.8, 62.1, 52.0 (OMe), 51.7 (OMe), 43.3, 33.0, 20.6.

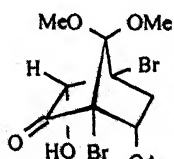


**Minor isomer 199c:**  $^1\text{H}$  NMR  $\delta$  4.63 (br s, 1H, carbinol H), 4.50 (dd, 1H,  $J=11.7, 3.4$  Hz), 4.35 (dd, 1H,  $J=11.7, 9.5$  Hz), 3.75 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.07-2.99 (m, 1H, one of the  $J=2.0$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.66 (dd, 1H,  $J=13.2, 11.9$  Hz, C(5) $\text{H}_{\text{exo}}$ ), 2.05 (s, 3H, OAc), 2.01 (br s, 1H, OH), 1.90 (dd, 1H,  $J=13.2, 5.4$  Hz, C(5) $\text{H}_{\text{endo}}$ );  $^{13}\text{C}$  NMR  $\delta$  201.5 (C=O), 171.0 (O-C=O), 103.0, 80.8 (carbinol C), 66.6, 64.4, 61.2, 51.98 (OMe), 51.9 (OMe), 44.5, 39.2, 20.9.



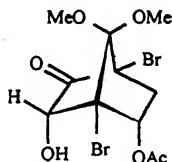
**Acyloin 198d,199d:** Yield 85%, mixture of regioisomers (80:20) in THF- $\text{H}_2\text{O}$ .

**Major isomer 198d:** Yield 63%, colorless solid, mp 95-96  $^\circ\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  5.38 (m, 1H, C(5) $\text{H}_{\text{exo}}$ ), 4.54 (dd, 1H,  $J=4.3, 2.1$  Hz, carbinol H), 3.75 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.44 (br s, 1H, OH), 2.86-2.80 (m, 1H, C(6) $\text{H}_{\text{exo}}$ ), 2.54 (dd, 1H,  $J=13.6, 3.2$  Hz, C(6) $\text{H}_{\text{endo}}$ ), 2.06 (s, 3H, OCOMe);  $^{13}\text{C}$  NMR  $\delta$  197.4 (C=O), 170.0 (O-C=O), 102.9, 79.2



(carbinol C), 74.6, 71.1, 60.4, 52.1 (2C), 37.6, 20.7; IR (KBr) 3350, 2900, 1740, 1710, 1420; Anal. Calcd for  $C_{11}H_{14}Br_2O_6$ : C 32.86, H 3.51, Found C 32.91, H 3.40.

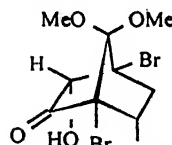
**Minor isomer 199d:** (From the mixture)  $^1H$  NMR  $\delta$  5.56 (dd, 1H,  $J=10.0, 2.0$  Hz, C(6)H<sub>exo</sub>), 4.57 (m, 1H, one of the  $J=2.0$ Hz, carbinol H), 3.74 (s, 3H, OMe), 3.70 (s, 3H, OMe), 3.01 (dd, 1H,  $J=14.1, 10.0$ Hz, C(5)H<sub>exo</sub>), 2.16 (s, 3H OCOMe), 1.95 (dd, 1H,  $J=14.1, 2.7$  Hz, C(5)H<sub>endo</sub>);  $^{13}C$  NMR  $\delta$  200.6 (C=O), 169.0 (O-C=O), 103.5, 78.3, 74.9, 67.6, 61.7, 51.98 (OMe), 51.96 (OMe), 41.8, 22.6.



**Acyloin 198f,199f:** Yield 68%, mixture of regioisomers (68:32).

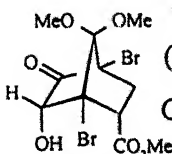
**Major isomer 198f:** separated from the mixture by crystallization in  $CHCl_3$ -Hexane, colourless solid, mp 125-126 °C,  $^1H$  NMR  $\delta$  4.47 (dd,

1H,  $J=9.2, 2.0$  Hz, carbinol H), 3.758 (s, 3H, OMe), 3.75 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.47 (dd, 1H,  $J=11.2, 4.1$  Hz, C(5)H<sub>exo</sub>), 2.70 (dd, 1H,  $J=13.2, 4.1$  Hz, C(6)H<sub>endo</sub>), 2.62 (dt, 1H,  $J=11.2, 2.0$  Hz, C(6)H<sub>exo</sub>);



$^{13}C$  NMR  $\delta$  198.6 (C=O), 173.3 (O-C=O), 103.4, 79.7, 70.7, 60.7, 53.4 (OMe), 52.3 (OMe), 52.0 (OMe), 50.4, 33.9; IR (KBr) 3300, 2900, 1760-1700 (br)  $cm^{-1}$ ; Anal. Calcd for  $C_{11}H_{14}Br_2O_6$ : C 32.86, H 3.51; Found C 32.78, H 3.48.

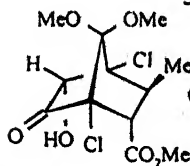
**Minor isomer 199f:** (from the mixture)  $^1\text{H}$  NMR  $\delta$  4.62 (br s, 1H, carbinol H), 3.76 (s, 3H, OMe), 3.757 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.56 (ddd, 1H,  $J=10.8, 6.5, 2.0$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.59-2.56 (m, 2H);  $^{13}\text{C}$  NMR  $\delta$  200.4 (C=O), 172.4 (O-C=O), 103.4, 80.8, 65.9, 63.0, 52.9 (OMe), 52.2 (OMe), 52.1 (OMe), 47.3, 36.2.



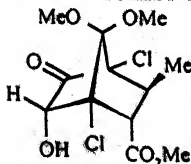
Irradiation of carbinol proton, C(2) $\text{H}_{\text{exo}}$  both in 198f, 199f resulted in the disappearance of W-coupling in C(6) $\text{H}_{\text{exo}}$  proton.

**Acyloin 200b,c:** Yield 75%, inseparable mixture of regioisomers (67:33), colourless solid, mp 94-107 °C; IR (KBr) 3300, 2900, 1760, 1200  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{12}\text{H}_{16}\text{Cl}_2\text{O}_6$ : C 40.06, H 4.93; Found C 40.21, H 4.89.

**Major isomer 200b:**  $^1\text{H}$  NMR  $\delta$  4.50 (d, 1H,  $J=7.1$  Hz, carbinol H), 3.74 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.54 (d, 1H,  $J=8.1$  Hz,  $\text{D}_2\text{O}$  exchangeable, OH), 3.08 (d, 1H,  $J=6.1$  Hz, C(5) $\text{H}_{\text{exo}}$ ), 2.90 (qn, 1H,  $J=7.1$  Hz, C(6) $\text{H}_{\text{endo}}$ ), 1.39 (s, 3H,  $J=7.1$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  198.7 (C=O), 171.8 (O-C=O), 103.4, 79.2 (carbinol C), 77.8, 72.7, 56.4, 53.1, 51.7 (OMe), 51.6 (OMe), 35.6, 17.6 (Me).

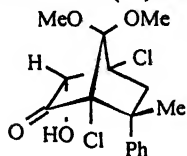


**Minor isomer 200c:**  $^1\text{H}$  NMR  $\delta$  4.54 (dd, 1H,  $J=6.5, 1.5$  Hz, carbinol H), 3.95 (br s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 3.78 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.20 (d, 1H,  $J=7.3$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.52 (qn, 1H,  $J=6.8$  Hz, C(6) $\text{H}_{\text{endo}}$ ).



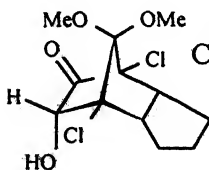
C(5)H<sub>endo</sub>), 1.32 (d, 3H,  $J=6.8$ Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  200.1 (C=O), 172.2 (O-C=O), 103.5, 79.6 (carbinol C), 77.6, 71.3, 54.5, 52.8, 51.6, 51.4, 38.2, 17.1 (Me).

**Acyloin 201b:** Yield 95%, colorless solid, mp 118-120 °C,  $^1\text{H}$  NMR  $\delta$  7.50-7.48 (m, 2H), 7.28-7.24 (m, 2H), 7.20-7.16 (m, 1H), 4.29 (d, 1H,  $J=2.0$ Hz, carbinol H), 3.75 (s, 3H, OMe), 3.60 (s, 3H, OMe), 3.48 (d, 1H,  $J=12.9$  Hz, C(6)H<sub>endo</sub>), 2.53 (dd, 1H,  $J=12.9, 2.0$  Hz, C(6)H<sub>exo</sub>), 1.69 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  199.4 (C=O), 143.1, 128.0, 126.8, 126.5, 103.2, 84.7, 77.1, 69.1, 51.3, 51.2, 46.3, 41.9, 29.9; IR (KBr) 3500, 2950, 1770, 1470, 1290 1200, 1090, 1040, 960  $\text{cm}^{-1}$ ; Anal. Calcd for C<sub>16</sub>H<sub>18</sub>Cl<sub>2</sub>O<sub>4</sub>: C 55.67, H 5.26; Found C, 55.43, H 5.31.

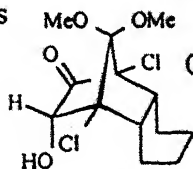


### Disubstituted Acyloins:

**Acyloin 200i:** Yield 100%, colorless solid, mp 111-113 °C,  $^1\text{H}$  NMR  $\delta$  4.64 (d, 1H,  $J=1.5$  Hz carbinol H), 3.64 (s, 3H, OMe), 3.56 (s, 3H, OMe), 3.19-3.12 (m, 1H, one of the  $J$  is 1.7 Hz, C(6)H<sub>exo</sub>), 3.02-2.97 (m, 1H, C(5)H<sub>exo</sub>), 2.30-2.24 (m, 1H), 1.67-1.47 (m, 5H);  $^{13}\text{C}$  NMR  $\delta$  202 (C=O), 105.2, 80.1 (carbinol C), 79.1, 71.2, 51.6, 51.3, 50.4, 50.0, 25.8, 25.4, 25.2; IR (KBr) 3400, 2900, 1740, 1420, 1400, 900  $\text{cm}^{-1}$ ; Anal. Calcd for C<sub>12</sub>H<sub>16</sub>Cl<sub>2</sub>O<sub>4</sub>: C 48.83, H 5.46; Found C 48.47, H 5.51.

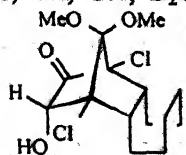


**Acylolin 200j:** Yield 100%, colorless solid, mp 133-134 °C,  $^1\text{H}$  NMR  $\delta$  4.62 (d, 1H,  $J=2$  Hz carbinol H), 3.65 (s, 3H, OMe), 3.56 (s, 3H, OMe), 3.41 (br s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.74-2.66 (m, 1H, one of the  $J$  is 2.0 Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 2.48 (ddd, 1H, 13.9, 12.3, 4.9 Hz,  $\text{C}(5)\text{H}_{\text{exo}}$ ), 2.02 (ddt, 1H,  $J_1=J_2=13.4$ ,  $J_3=3.6$  Hz), 1.68 (m, 2H), 1.55-1.45 (m, 2H), 1.36-1.29 (m, 1H), 1.21-1.13 (m, 1H), 0.97 (ddt, 1H,  $J=13.4$ , 13.3, 5.6 Hz);  $^{13}\text{C}$  NMR  $\delta$  201.8 (C=O), 103.1, 80.8 (carbinol C), 80.0, 72.5, 51.6 (2C), 44.5, 43.0, 19.7, 18.9, 18.4, 17.6; IR (KBr) 3400, 2900, 1760, 1440, 1080  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{13}\text{H}_{18}\text{Cl}_2\text{O}_4$ : C 50.50, H 5.87; Found C 49.69, H 5.56.



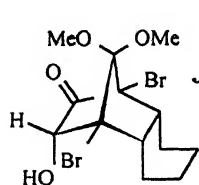
Irradiation of carbinol proton,  $\text{C}(2)\text{H}_{\text{exo}}$  in **200j** resulted in the disappearance of W-coupling in  $\text{C}(6)\text{H}_{\text{exo}}$  proton.

**Acylolin 200k:** Yield 100%, mp 168-170 °C,  $^1\text{H}$  NMR  $\delta$  4.55 (d, 1H,  $J=1.7$  Hz, carbinol H), 3.71 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.12 (br s, 1H, OH,  $\text{D}_2\text{O}$  exchangeable), 2.64 (t, 1H,  $J=10.9$  Hz), 2.52 (t, 1H,  $J=11.0$  Hz), 1.98-1.94 (m, 1H), 1.86-1.80 (m, 2H), 1.64-1.59 (m, 4H), 1.28-1.09 (m, 5H);  $^{13}\text{C}$  NMR  $\delta$  200.8 (C=O), 102.2, 80.6 (2C), 73.9, 51.74 (OMe), 51.70 (OMe), 48.1, 46.9, 31.0, 30.7, 25.8, 25.2, 23.4, 21.1; IR (KBr) 3300, 2800, 1740, 1420  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{15}\text{H}_{22}\text{O}_4\text{Cl}_2$ : C 53.42 H 6.58; Found C, 52.97, H 6.38.





**Acyloin 203:** Yield 54%, colorless solid, mp 138-139 °C;  $^1\text{H}$  NMR  $\delta$  4.66 (br s, 1H, carbinol H), 3.75 (s, 3H, OMe), 3.66 (s, 3H, OMe),

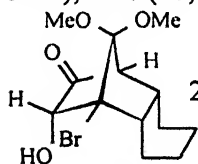


3.15 (br s, 1H, OH), 2.81-2.74 (m, 1H, one of the  $J=1.7$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.60-2.52 (m, 1H), 2.10-1.99 (m, 1H), 1.79-1.67 (m, 2H), 1.64-1.52 (m, 2H), 1.43-1.33 (m, 1H), 1.26-1.14 (m, 1H), 1.07-0.96 (m, 1H);  $^{13}\text{C}$

NMR  $\delta$  201.3 (C=O), 103.0, 81.7 (carbinol C), 73.4, 65.6, 51.9 (OMe), 51.8 (OMe), 46.3, 44.6, 19.9, 19.1, 18.9, 18.2; IR (KBr) 3400, 2900, 1750, 1100  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{13}\text{H}_{18}\text{Br}_2\text{O}_4$ : C 39.22, H 4.56; C39.31, H 4.61.

Irradiation of carbinol proton, C(2) $\text{H}_{\text{exo}}$  resulted in the disappearance of W-coupling in C(6) $\text{H}_{\text{exo}}$  proton.

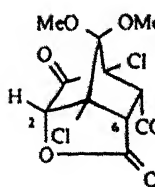
**Acyloin 204:** Yield 13%, obtained as a colorless solid, mp 54-55 °C,  $^1\text{H}$  NMR  $\delta$  4.63 (br s, 1H, carbinol H), 3.51 (s, 3H, OMe), 3.48 (s, 3H, OMe), 2.76 (dd, 1H,  $J=5.7, 1.7$  Hz, bridgehead H), 2.70 (br s, 1H, OH),



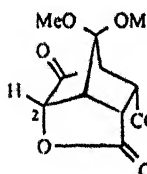
2.69-2.61 (m, 1H, one of the  $J=1.7$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.44-2.35 (m, 1H), 2.05 (dq, 1H,  $J=13.4, 3.7$  Hz), 1.74-1.66 (m, 2H), 1.62-1.58 (m, 1H), 1.39-1.33 (m, 2H),

1.21-1.10 (m, 2H);  $^{13}\text{C}$  NMR  $\delta$  207.0 (C=O), 105.2, 83.2 (carbinol C), 67.2, 57.5, 51.3 (OMe), 50.9 (OMe), 45.1, 35.2, 21.2, 19.9, 19.6, 17.9; IR (KBr) 3400, 2900, 1740, 1100  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{13}\text{H}_{19}\text{BrO}_4$ : C 48.92, H 6.00; Found C 49.01, H 5.96.

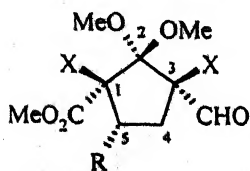
**Keto lactone 206:** Crude reaction mixture crystallized to give 83%, mp 165-167 °C,  $^1\text{H}$  NMR  $\delta$  4.77 (d, 1H,  $J=1.5$  Hz, C(2) $\text{H}_{\text{exo}}$ ), 3.90 (d, 1H,  $J=10.8$  Hz, C(5) $\text{H}_{\text{exo}}$ ), 3.74 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.65 (s, 3H, OMe), 3.44 (dd, 1H,  $J=10.8, 1.9$  Hz, C(6) $\text{H}_{\text{exo}}$ );  $^{13}\text{C}$  NMR  $\delta$  188.8 (C=O), 171.5 (O-C=O), 166.9 (O-C=O), 101.4 (C<sub>7</sub>), 83.53, 83.45, 72.1, 53.4 (OMe), 52.6 (OMe), 52.3 (OMe), 51.1, 49.7; IR 2900, 1700-1780 (br), 1420  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{12}\text{H}_{12}\text{Cl}_2\text{O}_7$ : C 42.50, H 3.57; Found C 42.04, H 3.65.



**Keto lactone 207:** Yield 71%, colorless solid, mp 110 °C, 4.63 (d, 1H, 5.4 Hz, C(2)H), 3.71 (s, 3H, OMe), 3.66-3.61 (m, 2H), 3.34 (s, 3H, OMe), 3.31 (s, 3H, OMe), 3.23 (dd, 1H,  $J=10.0, 5.1$  Hz), 3.04 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  198.7 (C=O), 175.0 (O-C=O), 169.5 (O-C=O), 106.5, 79.8, 54.3, 52.8, 51.6, 50.5, 48.9, 45.5, 41.0; IR (KBr) 2900, 1760, 1700, 1300  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{12}\text{H}_{14}\text{O}_7$ : C 53.35, H 5.22; Found C 53.21, H 5.16.

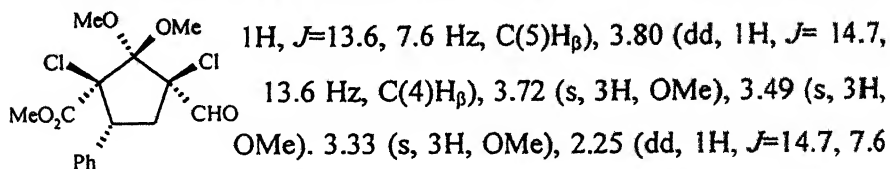


### Cyclopentane carboxaldehydes:



**Cyclopentane derivative 213a:** Yield 75%, colorless viscous liquid,

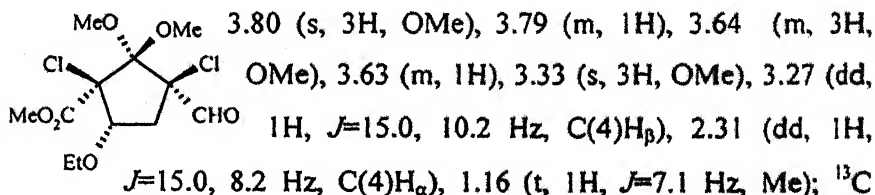
$^1\text{H}$  NMR  $\delta$  9.56 (s, 1H, CHO), 7.34-7.26 (m, 5H, aromatic), 4.05 (dd,



Hz, C(4) $\text{H}_\alpha$ );  $^{13}\text{C}$  NMR  $\delta$  189.1 (CHO), 167.0 (O-C=O), 134.7, 128.3, 128.2, 110.7, 81.8, 79.6, 53.3, 53.1, 53.0, 52.9, 37.3; IR (neat) 2900, 1720, 1330, 800  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{16}\text{H}_{18}\text{Cl}_2\text{O}_5$ : C 53.20, H 5.02; Found C 53.12, H 5.09.

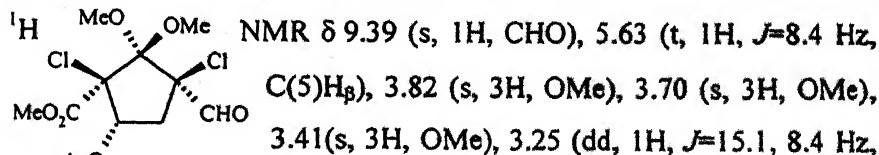
**Cyclopentane derivative 213b:** Yield 77%, colorless viscous liquid,

$^1\text{H}$  NMR  $\delta$  9.44 (s, 1H, CHO), 4.43 (dd, 1H,  $J=10.2$ , 8.2 Hz, C(5) $\text{H}_\alpha$ ),



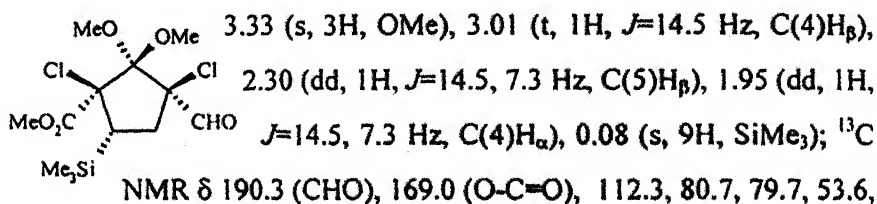
NMR  $\delta$  188.4 (CHO), 166.4 (O-C=O), 108.7, 85.2, 80.4, 78.6, 67.1, 53.4, 53.1, 53.0, 38.7, 15.3; IR (neat) 2900, 1760, 1700, 1330  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{12}\text{H}_{18}\text{Cl}_2\text{O}_6$ : C 43.79, H 5.51; Found C 43.85, H 5.62.

**Cyclopentane derivative 213d:** Yield 83%, colorless viscous liquid,

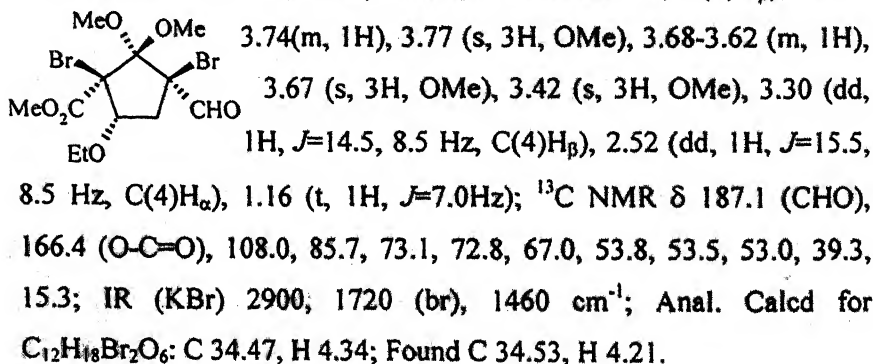


C(4) $H_\beta$ ), 2.56 (dd, 1H,  $J=15.1, 8.6$  Hz, C(4) $H_\alpha$ ), 2.07 (s, 3H, OMe);  $^{13}\text{C}$  NMR  $\delta$  187.3 (CHO), 169.4 (O-C=O), 165.8 (O-C=O), 108.4, 77.9, 77.71, 77.68, 53.5 (OMe), 53.3 (OMe), 53.1 (OMe), 37.5, 20.6; IR (neat) 2900, 1740 (br), 1710, 1380  $\text{cm}^{-1}$ . Anal. Calcd for  $\text{C}_{12}\text{H}_{16}\text{C}_2\text{O}_7$ : C 42.00, H 4.70; Found C 41.96, H 4.64.

**Cyclopentane derivative 213e:** Yield 71%, colorless solid, mp 69 °C,  $^1\text{H}$  NMR  $\delta$  9.53 (s, 1H, CHO), 3.75 (s, 3H, OMe), 3.57 (s, 3H, OMe),

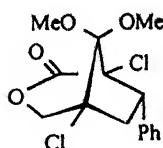


**Cyclopentane derivative 215b:** Yield 78%, colorless viscous liquid,  $^1\text{H}$  NMR  $\delta$  9.43(s, 1H, CHO), 4.55 (t, 1H,  $J=8.4$  Hz, C(5) $H_\beta$ ), 3.81-



**1,5-Dichloro-8,8-dimethoxy-7-phenyl-3-oxa-bicyclo[3.2.1]octan-2-one 214:** Yield 25%, colorless solid, mp 140-142 °C,  $^1\text{H}$  NMR  $\delta$  7.32

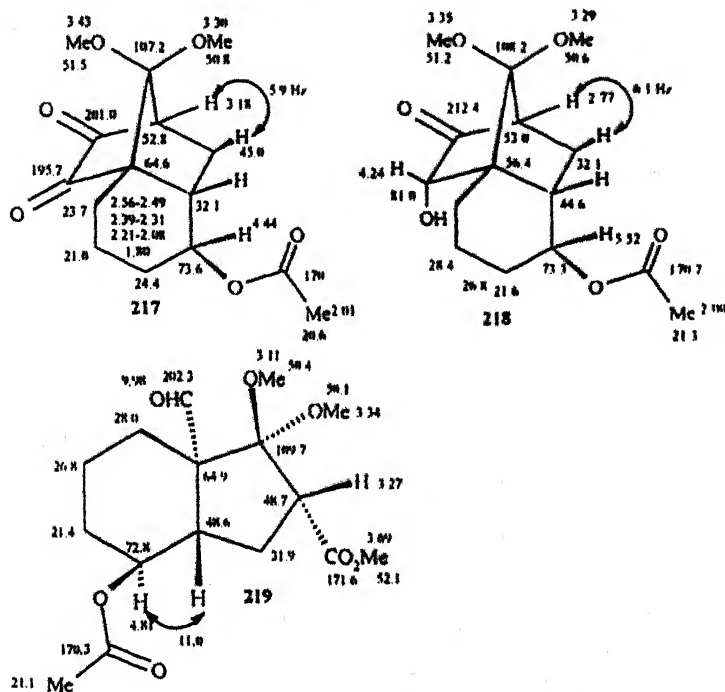
(s, 5H, aromatic), 4.56 (d, 1H,  $J=10.0$  Hz), 4.30 (d, 1H,  $J=10.3$  Hz), 3.89 (dd, 1H,  $J=12.7, 6.8$  Hz), 3.85 (s, 3H, OMe), 3.67 (s, 3H, OMe), 2.97 (t, 1H,  $J=14.1$  Hz), 2.63 (dd, 1H,  $J=14.1, 6.8$  Hz);  $^{13}\text{C}$  NMR  $\delta$  165.1 (O=C=O), 134.7, 128.8, 128.5, 128.4, 102.4, 81.2, 74.6, 67.2, 53.2, 52.5, 51.7, 41.0; IR (KBr) 2950, 1740, 1440, 1380, 1300  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{15}\text{H}_{16}\text{Cl}_2\text{O}_4$ : C 54.40, H 4.87; Found C 54.71, H 4.67.



**Diketone 216:** Yield: 84%;  $^1\text{H}$  NMR  $\delta$  4.47-4.40 (m, 1H), 3.43 (s, 3H, OMe), 3.30 (s, 3H, OMe), 3.18 (d, 1H,  $J=5.9$  Hz, bridgehead H), 2.56-2.49 (m, 1H), 2.39-2.31 (m, 1H), 2.21-2.08 (m, 3H), 2.01 (s, 3H, OAc), 1.81-1.78 (m, 1H), 1.70-1.62 (m, 1H), 1.53-1.48 (m, 1H), 1.29-1.19 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  201.0, 195.7, 170.2, 107.2, 73.6, 64.6, 52.8, 51.5, 50.8, 45.0, 32.1, 24.4, 23.7, 21.0, 20.6; IR (neat) 2900, 1750, 1720, 1440, 1360  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{15}\text{H}_{20}\text{O}_6$ : C 60.80, H 6.80; ; Found C 60.85, H 6.83.

**Acylolin 217:** Yield: 43%;  $^1\text{H}$  NMR  $\delta$  5.52 (ddd, 1H,  $J=11.6, 10.3, 4.9$  Hz), 4.24 (d, 1H,  $J=1.0$  Hz), 3.35 (s, 3H, OMe), 3.29 (s, 3H, OMe), 2.77 (dd, 1H,  $J=6.1, 1.4$  Hz), 2.50-2.43 (m, 1H), 2.19 (ddd, 1H,  $J=13.7, 10.0, 6.4$  Hz), 2.14-2.10 (m, 2H), 2.05 (td, 1H,  $J=13.4, 4.2$  Hz), 2.00 (s,

3H, OAc), 1.96-1.95 (m, 1H), 1.82 (dt, 1H,  $J=13.2, 4.4$  Hz), 1.73-1.68 (m, 1H), 1.43 (dd, 1H,  $J=13.9, 7.6$  Hz), 1.22-1.12 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  212.4, 170.7, 108.2, 81.0, 73.3, 56.4, 53.0, 51.2, 50.6, 44.6, 32.1, 28.4, 26.8, 21.6, 21.3; IR (neat) 3400, 2900, 1740, 1460  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{15}\text{H}_{22}\text{O}_6$ : C 60.39, H 7.43; Found C 60.44, H 7.46.



**Transhyrindane derivative 219:** Yield: 51%;  $^1\text{H}$  NMR  $\delta$  9.98 (s, 1H, CHO), 4.81 (dt, 1H,  $J=11.0, 4.4$  Hz), 3.69 (s, 3H, OMe), 3.34 (s, 3H, OMe), 3.31-3.26 (m, 1H), 3.11 (s, 3H, OMe), 2.63-2.53 (m, 1H), 2.15-2.05 (m, 4H), 2.03-1.98 (m, 1H), 2.01 (s, 3H, OAc), 1.70-1.63 (m, 1H), 1.58-1.57 (m, 1H), 1.26-1.15 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  202.3, 171.6, 170.3, 109.7, 72.8, 64.9, 52.1, 50.4, 50.1, 48.7, 48.6, 31.9, 28.0, 26.8, 21.4,

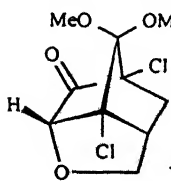
21.1; IR (neat) 2900, 1720, 1700, 1450  $\text{cm}^{-1}$ ; Anal. calcd. for  $\text{C}_{16}\text{H}_{24}\text{O}_7$ : C 58.53, H 7.37; Found C 58.59, H 7.40.

**1,7-Dichloro-8,8-dimethoxy-4-oxa-tricyclo[4.2.1.0<sup>3,7</sup>]nonane-6,9-diol 196g:** (For its preparation in different route see<sup>12</sup>) Yield 59%, mp 119–

120 °C;  $^1\text{H}$  NMR  $\delta$  4.27 (dd, 1H,  $J=6.2, 2.4$  Hz, carbinol H), 4.23 (dd, 1H,  $J=8.3, 3.9$  Hz), 3.71 (d, 1H,  $J=8.3$  Hz), 3.65 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.45 (br s, 1H,  $J=6.2$  Hz, OH,  $\text{D}_2\text{O}$  exchangeable), 3.06 (d, 1H,  $J=6.5$  Hz, OH,  $\text{D}_2\text{O}$  exchangeable), 2.73 (ddd, 1H,  $J=11.0, 3.9, 2.2$  Hz,  $\text{C}(5)\text{H}_{\text{exo}}$ ), 2.44 (ddd, 1H,  $J=12.5, 11.0, 2.4$  Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 2.08 (dd, 1H,  $J=12.5, 2.2$ ,  $\text{C}(6)\text{H}_{\text{endo}}$ );  $^{13}\text{C}$  NMR  $\delta$  105.3, 102.2, 78.8 (carbinol C), 77.1, 71.0, 70.5, 51.6 (OMe), 51.2 (OMe), 45.5, 35.7; IR (KBr) 3300, 2850, 1200  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{10}\text{H}_{14}\text{Cl}_2\text{O}_5$ : C 42.13, H 4.95; Found C 42.05, H 4.91.

**1,7-Dichloro-8,8-dimethoxy-4-oxa-tricyclo[4.2.1.0<sup>3,7</sup>]nonan-2-one**

**120a:** Yield 8%, mp 68–70 °C,  $^1\text{H}$  NMR  $\delta$  4.39 (dd, 1H,  $J=8.8, 4.2$  Hz), 4.29 (br s, 1H), 3.95 (d, 1H,  $J=8.8$  Hz), 3.71 (s, 3H, OMe), 3.62 (s, 3H, OMe), 2.93 (m, 1H), 2.70 (dd, 1H,  $J=12.7, 11.1$  Hz), 1.74 (dd, 1H,  $J=12.7, 2.0$  Hz);  $^{13}\text{C}$

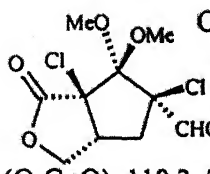


NMR  $\delta$  198.0 ( $\text{C}=\text{O}$ ), 102.3, 86.7, 75.4, 75.2, 74.2, 52.2 (OMe), 51.9 (OMe), 45.5, 37.0; IR (KBr) 2850, 1760, 1240  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{10}\text{H}_{12}\text{Cl}_2\text{O}_4$ : C 44.97, H 4.53; Found C 44.53, H 4.57.

For compound 139, see Ch1C, page no. 224.

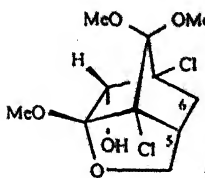
**5,6a-Dichloro-6,6-dimethoxy-1-oxo-hexahydro-cyclopenta[c]furan-5-carbaldehyde 213g:** (For its preparation indifferent route see<sup>12</sup>)

Yield 91%; colorless solid; mp 120-122 °C; <sup>1</sup>H NMR δ 9.58 (s, 1H, CHO), 4.63 (t, 1H, *J*=9.2 Hz), 4.13 (dd, 1H, *J*=9.2, 4.4 Hz), 3.74 (s, 3H, OMe), 3.52 (ddt, 1H, *J*=9.4, 8.6, 4.6 Hz), 3.33 (s, 3H, OMe), 2.71 (dd, 1H, *J*=14.6, 8.0 Hz), 2.47 (dd, 1H, *J*=14.9, 9.5 Hz); <sup>13</sup>C NMR δ 189.4 (CHO), 170.9 (O-C=O), 110.3, 79.7, 73.5, 71.3, 54.0, 53.0, 46.7, 37.7; IR (KBr) 2900, 1750, 1720, 1380 cm<sup>-1</sup>; Anal. calcd for C<sub>10</sub>H<sub>12</sub>Cl<sub>2</sub>O<sub>5</sub>: C 42.43, H 4.27; Found: C 42.48, H 4.21.



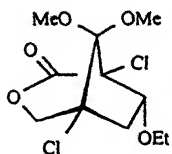
**1,7-Dichloro-6,8,8-trimethoxy-4-oxa-tricyclo[4.2.1.0<sup>3,7</sup>]nonan-9-ol**

**220:** Yield 65%, mp 73-75 °C; <sup>1</sup>H NMR δ 4.30-4.25 (m, 2H), 3.77 (d, 1H, *J* = 8.6 Hz), 3.65 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.50 (s, 3H, OMe), 3.13 (d, 1H, *J* = 8.1 Hz, OH, D<sub>2</sub>O exchangeable), 2.68 (ddd, 1H, *J* = 11.0, 2.7, 2.2 Hz, C(5)H<sub>exo</sub>), 2.42 (ddd, 1H, *J* = 12.4, 11.0, 2.0 Hz, C(6)H<sub>exo</sub>), 1.98 (dd, 1H, *J* = 12.4, 2.1 Hz C(6)H<sub>endo</sub>); <sup>13</sup>C NMR δ 105.3, 102.2, 78.8 (carbinol C), 77.1, 71.0, 70.5, 51.6 (OMe), 51.2 (OMe), 45.5, 35.7; IR (KBr) 3300, 2850, 1440, 1200 cm<sup>-1</sup>; Anal. Calcd for C<sub>11</sub>H<sub>16</sub>Cl<sub>2</sub>O<sub>5</sub>: C 56.19, H 6.86; Found C 56.23, H 6.89.





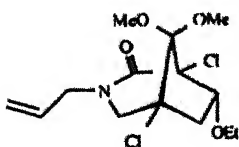
**1,5-Dichloro-7-ethoxy-8,8-dimethoxy-3-oxa-bicyclo[3.2.1]octan-2-one 221:** Yield 95%, colorless solid, mp 82-84 °C;  $^1\text{H}$  NMR  $\delta$  4.45 (dd, 1H,  $J = 10.2, 2.1$  Hz), 4.23 (dd, 1H,  $J = 10.7, 3.2$  Hz), 4.14 (d, 1H,  $J = 10.2$  Hz), 3.81 (dq, 1H,  $J = 9.3, 6.8$  Hz, -O-CH<sub>2</sub>-), 3.73 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.53 (dq, 1H,  $J = 9.3, 6.8$  Hz, -O-CH<sub>2</sub>-), 2.93 (ddd, 1H,  $J_1 = J_2 = 12.4$  Hz,  $J_3 = 2.2$  Hz), 2.19 (dd, 1H,  $J = 14.1, 3.4$  Hz), 1.15 (t, 1H,  $J = 6.8$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  164.4 (O-C=O), 101.6, 83.3, 79.9, 73.9, 67.3, 67.1, 52.9, 52.6, 43.4, 15.2; IR (KBr) 2900, 1760, 1430, 1320  $\text{cm}^{-1}$ ; Anal. calcd for  $\text{C}_{14}\text{H}_{20}\text{Cl}_2\text{O}_5$ : C 49.57, H 5.94; Found: C 49.61, H 5.98.



**3-Allyl-1,5-dichloro-7-ethoxy-8,8-dimethoxy-3-aza-**

**bicyclo[3.2.1]octan-2-one 222:** The aldehyde **213b** (73 mg, 0.23 mmol) was dissolved in 3 ml of benzene and 0.46 mmol (26 mg) of allyl amine was added to that along with few pieces of 4 Å molecular sieves. The reaction mixture was stirred at room temperature for 2 h (till the completion of starting material as per tlc). Benzene was evaporated at room temperature in vacuum and dried. The residue was dissolved in MeOH and cooled to 0 °C and 15 mg (0.40 mmol) of  $\text{NaBH}_4$  was added and stirred for 1 h. MeOH was evaporated at room temperature and water 5 ml was added and extracted with ethyl acetate. Combined organic layer was washed with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and concentrated. Purification by silica gel column chromatography (20-25% ethyl acetate-hexane) afforded 50 mg (64%) of the pure amide **222**.

Yield 64%; colorless solid; mp 140-142 °C;  $^1\text{H}$  NMR  $\delta$  5.81-5.71 (m, 1H, olefinic), 5.28 (d, 1H,  $J = 17.3$  Hz, olefinic), 5.17 (d, 1H,  $J = 10.2$  Hz, olefinic), 5.02 (d, 1H,  $J = 5.8$  Hz, C(7) $\text{H}_{\text{exo}}$ ), 4.37-4.32 (m, 1H),



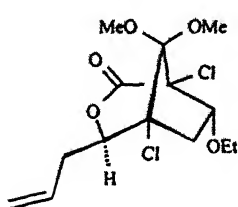
4.19 (dd, 1H,  $J = 8.8, 5.3$  Hz), 3.96 (dd, 1H,  $J = 15.3, 7.1$  Hz), 3.78 (dq, 1H,  $J = 9.3, 7.1$  Hz, -O-CH<sub>2</sub>-), 3.70 (s, 3H, OMe), 3.51 (s, 3H, OMe), 3.49-3.45 (m, 1H, -O-CH<sub>2</sub>-), 3.08 (d,

1H,  $J = 6.1$  Hz), 2.55-2.53 (m, 2H), 1.09 (t, 1H,  $J = 7.1$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  162.8 (N-C=O), 131.9, 117.9, 102.3, 83.2, 83.1, 80.1, 74.8, 66.9, 52.8 (OMe), 52.6 (OMe), 46.0, 37.1, 15.2 (Me); IR (KBr) 2900, 1650, 1420, 1300, 1240, 1200  $\text{cm}^{-1}$ ; Anal. calcd for  $\text{C}_{14}\text{H}_{21}\text{Cl}_2\text{NO}_4$ : C 49.72, H 6.26, N 4.14; Found: C 42.78, H 6.30, N 4.17.

**General procedure for allylindium addition to aldehydes:** To a solution of aldehyde 213 (0.5 mmol), in 1 ml DMF was added indium metal (0.75 mmol, cut into small pieces) and allyl bromide (1 mmol), and stirred at room temperature for the specified time (Scheme 11). After completion of the reaction, as monitored by tlc, the reaction mixture was quenched with few drops of 5% HCl and extracted with diethyl ether. The combined organic layer was washed once with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated. The resulting residue was purified by silica gel column chromatography to provide the pure homoallylic alcohols. In each case, the  $^1\text{H}$  NMR of the crude product, before column purification was taken to record the product distribution.

**4-Allyl-1,5-dichloro-7-ethoxy-8,8-dimethoxy-3-oxa-**

**bicyclo[3.2.1]octan-2-one 223b:** Yield 95%, obtained as viscous liquid;  $^1\text{H}$  NMR (500 MHz),  $\delta$  6.00–5.89 (m, 1H, olefinic), 5.17 (d, 1H,  $J = 15.0$  Hz, olefinic), 5.14 (d, 1H,  $J = 8.8$  Hz, olefinic), 4.35 (dd, 1H,  $J = 10.5, 2.0$  Hz), 4.21 (dd, 1H,  $J = 10.7, 3.0$  Hz), 3.81 (dq, 1H,  $J = 9.3,$

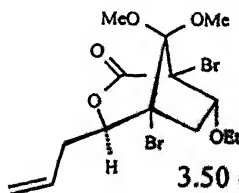


7.1 Hz,  $-\text{O}-\text{CH}_2-$ ), 3.73 (s, 3H, OMe), 3.60 (s, 3H, OMe), 3.55 (dq, 1H,  $J = 9.3, 7.1$  Hz,  $-\text{O}-\text{CH}_2-$ ), 3.00 (dd, 1H,  $J = 14.2, 10.7$  Hz), 2.91 (dd, 1H,  $J = 13.9, 6.9$  Hz), 2.78–2.69 (m, 1H), 2.18 (dd, 1H,  $J = 14.1, 3.2$  Hz), 1.14 (t, 1H,  $J =$

7.1 Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  163.6 (O-C=O), 134.6, 117.9, 102.3, 87.9, 83.5, 80.1, 79.9, 70.0, 67.2, 52.9, 52.6, 47.3, 37.4, 15.2; IR (KBr) 2900, 1770, 1630, 1420, 1300  $\text{cm}^{-1}$ ; Anal. calcd for  $\text{C}_{14}\text{H}_{20}\text{Cl}_2\text{O}_5$ : C 49.57, H 5.94; Found: C 49.61, H 5.98.

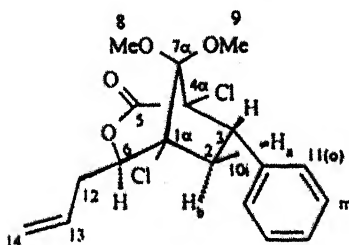
**4-Allyl-1,5-dibromo-7-ethoxy-8,8-dimethoxy-3-oxa-**

**bicyclo[3.2.1]octan-2-one 225b:** Yield 94%, obtained as viscous liquid;  $^1\text{H}$  NMR  $\delta$  5.92–5.82 (m, 1H, olefinic), 5.12–5.03 (m, 2H, olefinic), 4.30 (dd, 1H,  $J = 10.8, 1.7$  Hz), 4.23 (dd, 1H,  $J = 10.4, 3.0$  Hz), 3.79 (dq, 1H,  $J = 9.3, 7.1$  Hz,  $-\text{O}-\text{CH}_2-$ ), 3.70 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.50 (dq, 1H,  $J = 9.3, 7.1$  Hz,  $-\text{O}-\text{CH}_2-$ ), 3.06 (dd, 1H,  $J = 14.2, 10.5$  Hz), 2.98 (dd, 1H,  $J = 14.6, 7.3$  Hz), 2.73–2.65 (m, 1H), 2.18



(dd, 1H,  $J = 14.2, 3.2$  Hz), 1.10 (t, 1H,  $J = 7.1$  Hz, Me);  $^{13}\text{C}$  NMR  $\delta$  163.3 (O-C=O), 134.8, 117.8, 102.5, 88.4, 84.9, 72.4 (bridgehead), 67.3, 62.6 (bridgehead), 53.11 (OMe), 53.08 (OMe), 49.1, 39.1, 15.2; IR (KBr) 2900, 1760, 1620, 1440, 1360  $\text{cm}^{-1}$ ; Anal. calcd for  $\text{C}_{14}\text{H}_{20}\text{Cl}_2\text{O}_5$ : C 39.28, H 4.71; Found: C 39.34, H 4.75.

**Oxa-bicyclo[3.2.1] octanaone 223a:** Colorless solid, mp 121-122  $^{\circ}\text{C}$ ;  
 $^1\text{H}$  NMR (500 MHz)  $\delta$  7.35-7.29 (m, 5H, aromatic), 6.03-5.93 (m, 1H,

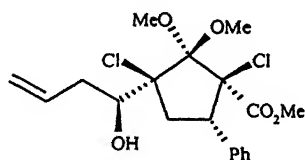


olefinic, CH), 5.24-5.17 (m, 2H, olefinic,  $\text{CH}_2$ ), 4.52 (dd, 1H,  $J = 12.5, 2.0$ ,  $\text{H}_6$ ), 3.88 (dd, 1H,  $J = 12.8, 6.4$  Hz,  $\text{H}_3$ ), 3.84 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.06 (dd, 1H,  $J = 14.2, 12.7$  Hz,  $\text{C}(2)\text{H}_{\text{exo}}$ ), 3.02-2.97 (m, 1H,

allylic  $\text{CH}_2$ ), 2.84-2.76 (m, 1H, allylic  $\text{CH}_2$ ), 2.61 (dd, 1H,  $J = 14.2, 6.4$  Hz,  $\text{C}(2)\text{H}_{\text{endo}}$ );  $^{13}\text{C}$  NMR  $\delta$  164.3 (O-C=O), 134.7 ( $\text{C}_{13}$ ), 134.6 ( $\text{C}_{10i}$ ), 128.8, 128.3, 117.1 ( $\text{C}_{14}$ ), 111.1 ( $\text{C}_{7\alpha}$ ), 89.1 ( $\text{C}_6$ ), 81.3 ( $\text{C}_{4\alpha}$ ), 70.2 ( $\text{C}_{1\alpha}$ ), 72.4 (bridgehead), 53.1 ( $\text{C}_9$ ), 52.7 ( $\text{C}_8$ ), 51.8 ( $\text{C}_3$ ), 45.0 ( $\text{C}_2$ ), 37.2 ( $\text{C}_{12}$ ); IR (KBr) 2950, 1770, 1620, 1430  $\text{cm}^{-1}$ ; Anal. calcd for  $\text{C}_{18}\text{H}_{20}\text{Cl}_2\text{O}_4$ : C 58.23, H 5.43; Found: C 58.28, H 5.46.

**1,3-Dichloro-3-(1-hydroxy-but-3-enyl)-2,2-dimethoxy-5-phenyl cyclopentanecarboxylic acid methyl ester 224a:** Colorless viscous liquid,  $^1\text{H}$  NMR  $\delta$  7.34-7.24 (m, 5H, aromatic), 6.10-5.96 (m, 1H,

olefinic), 5.27-5.10 (m, 2H, olefinic), 4.44-4.40 (m, 1H, carbinol hydrogen), 3.89 (dd, 1H,  $J = 14.3, 6.0$ ,  $H_5$ ), 3.64 (s, 3H, OMe), 3.52 (s, 3H, OMe), 3.33 (s, 3H, OMe), 3.22-3.15 (m, 1H), 2.55-2.47 (m, 1H), 2.36 (dd, 1H,  $J = 14.0, 6.4$  Hz, allylic  $CH_2$ ), 2.21 (dd, 1H,  $J = 13.9, 6.1$



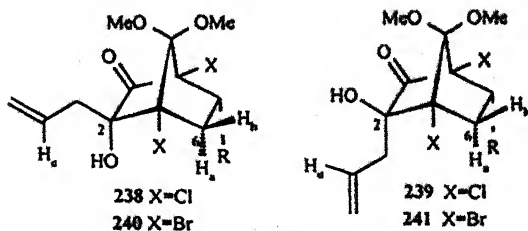
Hz,  $C(4)H_\beta$ );  $^{13}C$  NMR  $\delta$  167.6 (O-C=O), 135.5, 134.6, 128.5, 128.3, 117.1 ( $C_{14}$ ), 111.1 ( $C_{7\alpha}$ ), 85.8 (carbinol carbon), 82.5, 73.6, 53.0 (OMe), 52.8 (OMe), 52.7

(OMe), 52.4 ( $C_5$ ), 43.2 ( $C_2$ ), 36.8 (allylic  $\underline{CH_2}$ ); IR (KBr) 2900, 170, 1620, 1430  $cm^{-1}$ ; Anal. calcd for  $C_{19}H_{23}Cl_2O_5$ : C 56.73, H 5.76; Found: C 56.77, H 5.79.

## Chapter 3B

Diastereoselection During Allylindium Addition to Norbornyl  $\alpha$ -Diketones

**General procedure for the indium mediated allylation of  $\alpha$ -diketones:** A mixture of  $\alpha$ -diketone (1 mmol), indium metal (1.5 mmol, cut into small pieces) and allyl bromide (2.25 mmol) in DMF (1ml) was stirred at room temperature for the specified time (Table 1, 2). After completion of the reaction, as monitored by tlc, the reaction mixture was quenched with few drops of 5% HCl and extracted with diethyl ether. The combined organic layer was washed once with brine, dried over anhydrous  $\text{Na}_2\text{SO}_4$  and evaporated. The resulting residue was purified by silica gel column chromatography to provide the pure homoallylic alcohols. In each case, the  $^1\text{H}$  NMR of the crude product, before column purification was taken to record the product distribution.

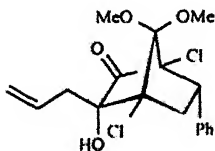


**Spectral Data For Monosubstituted Acyloins 238-240:** The carbinol hydrogen is assigned as  $\text{C}_2$  in all the mono and disubstituted acyloins to compare the  $^1\text{H}$  NMR (400 MHz) values of *exo* and *endo* protons on the

carbon C<sub>6</sub> and C<sub>5</sub> with those of the parent  $\alpha$ -diketone for a comparison the regio- and stereo-selectivity for the formation of major isomer.

**Acylolin 238a,239a:** Yield 94%, mixture of regioisomers (82:18).

**Major isomer 238a:** colorless solid, mp 118-120 °C, <sup>1</sup>H NMR  $\delta$  7.39-7.24 (m, 5H, aromatic), 6.22-6.13 (m, 1H, olefinic), 5.42 (d, 1H, *J* = 10.0 Hz, olefinic), 5.37 (d, 1H, *J* = 17.1 Hz, olefinic), 3.77 (s, 3H,

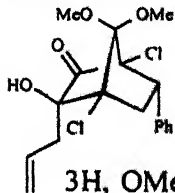


OMe), 3.71 (dd, 1H, *J* = 12.4, 5.4 Hz, C(5)H<sub>exo</sub>), 3.65 (s, 3H, OMe), 3.17 (s, 1H, D<sub>2</sub>O exchangeable, OH), 3.13 (dd, 1H, *J* = 12.8, 5.5 Hz, C(6)H<sub>endo</sub>), 2.97 (d ½ AB q, *J* = 13.8, 5.4 Hz,

allylic CH<sub>2</sub>), 2.76 (dd, 1H, *J*<sub>1</sub> = *J*<sub>2</sub> = 12.7 Hz, C(6)H<sub>exo</sub>), 2.74 (d ½ AB q, *J* = 13.9, 10.0 Hz, allylic CH<sub>2</sub>);  $\delta$  202.0 (-C=O), 135.4, 131.7, 129.4, 128.1, 127.7, 123.1, 103.5, 81.6, 78.5 (carbinol C), 73.5, 51.6 (2C, OMe), 48.1, 39.8, 37.4; IR (KBr) 3500, 2950, 1770, 1610, 1100 cm<sup>-1</sup>; Anal. Calcd. for C<sub>18</sub>H<sub>20</sub>Cl<sub>2</sub>O<sub>4</sub>: C 58.23, H 5.43; Found C 58.29, H 5.47.

Irradiation of the olefinic proton at 6.22-6.13 (m, 1H, olefinic) carried out to assign the allylic CH<sub>2</sub> and C(6)H<sub>exo</sub> protons. Two protons, one of the allylic CH<sub>2</sub> and C(6)H<sub>exo</sub> protons appeared as a multiplet.

**Minor isomer 239a:** <sup>1</sup>H NMR  $\delta$  7.32-7.21 (m, 5H, aromatic), 5.98-5.88

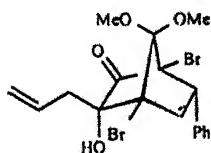


(m, 1H, olefinic), 5.07 (d, 1H, *J* = 10.0 Hz, olefinic), 4.83 (d, 1H, *J* = 17.1 Hz, olefinic), 4.05 (dd, 1H, *J* = 13.0, 4.2 Hz, C(5)H<sub>exo</sub>), 3.77 (s, 3H, OMe), 3.68 (s, 3H, OMe), 3.20 (dd, 1H, *J*<sub>1</sub> = *J*<sub>2</sub> = 13.0 Hz C(6)H<sub>exo</sub>), 2.46 (dd,

1H,  $J = 13.0, 4.2$  Hz, C(6)H<sub>endo</sub>), 2.16-2.06 (m, 2H, allylic CH<sub>2</sub>);  $\delta$  203.1 (-C=O), 137.8, 130.7, 128.7, 127.2, 126.9, 119.2, 105.4, 80.4 (carbinol C), 80.0, 72.7, 52.4 (OMe), 52.1 (OMe), 44.8, 39.7, 36.6.

**Acylain 240a, 241a:** Yield 93%, mixture of regioisomers (89:11).

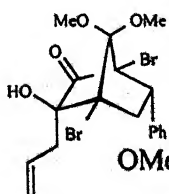
**Major isomer 240a:** colorless solid, mp 78-80 °C, <sup>1</sup>H NMR  $\delta$  7.37-7.22 (m, 5H, aromatic), 6.23-6.13 (m, 1H, olefinic), 5.43 (d, 1H,  $J = 10.4$  Hz, olefinic), 5.39 (d, 1H,  $J = 17.2$  Hz, olefinic), 3.81 (s, 3H, OMe), 3.73 (dd, 1H,  $J = 12.6, 5.5$  Hz, C(5)H<sub>exo</sub>), 3.69 (s, 3H, OMe),



3.22 (dd, 1H,  $J = 12.6, 5.4$  Hz, C(6)H<sub>endo</sub>), 3.21 (s, 1H, D<sub>2</sub>O exchangeable, OH), 2.99 (d ½ AB q, 1H,  $J = 13.6, 5.2$  Hz, allylic CH<sub>2</sub>), 2.89 (dd, 1H,  $J_1 = J_2 = 12.7$  Hz, C(6)H<sub>exo</sub>), 2.71 (d ½ AB q,  $J = 13.6,$

10.0 Hz, allylic CH<sub>2</sub>);  $\delta$  201.0 (-C=O), 136.7, 131.8, 129.5, 128.0, 127.7, 123.1, 103.6, 78.8 (carbinol C), 76.1, 67.2, 51.7 (OMe), 51.6 (OMe), 49.4, 41.8, 39.6; IR (KBr) 3500, 2950, 1780, 1610 cm<sup>-1</sup>; Anal. Calcd. for C<sub>18</sub>H<sub>20</sub>Br<sub>2</sub>O<sub>4</sub>: C 46.98, H 4.38; Found C 47.03, H 4.35.

**Minor isomer 241a:** <sup>1</sup>H NMR  $\delta$  7.32-7.21 (m, 5H, aromatic), 6.02-5.92



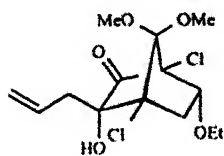
(m, 1H, olefinic), 5.09 (d, 1H,  $J = 10.0$  Hz, olefinic), 4.85 (d, 1H,  $J = 17.0$  Hz, olefinic), 4.08 (dd, 1H,  $J = 13.1, 4.2$  Hz, C(5)H<sub>exo</sub>), 3.82 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.30 (dd, 1H,  $J_1 = J_2 = 13.1$  Hz, C(6)H<sub>exo</sub>), 2.50 (dd, 1H,  $J = 13.1, 4.2$  Hz, C(6)H<sub>endo</sub>), 2.19-2.10 (m, 2H, allylic CH<sub>2</sub>);  $\delta$



202.5 (-C=O), 138.1, 130.7, 129.8, 128.7, 127.1, 119.3, 105.7, 80.4 (carbinol C), 73.3, 66.7, 52.7 (OMe), 52.3 (OMe), 44.8, 39.7, 36.6.

**Acyloin 238b, 239b:** Yield 93%, mixture of regioisomers (14:86).

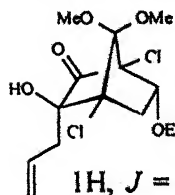
**Minor isomer 238b:**  $^1\text{H}$  NMR  $\delta$  6.28-6.18 (m, 1H, olefinic), 5.29 (d, 1H,  $J = 10.0$  Hz, olefinic), 5.25 (d, 1H,  $J = 17.3$  Hz, olefinic), 4.13 (dd, 1H,  $J = 9.3, 2.2$  Hz, C(5) $\text{H}_{\text{exo}}$ ), 3.68 (dq, one of  $J = 6.9$  Hz, merged with



OMe, -O-CH<sub>2</sub>), 3.67 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.53 (dq, 1H,  $J = 9.5, 7.1$  Hz, -O-CH<sub>2</sub>), 3.15 (s, 1H, D<sub>2</sub>O exchangeable, OH), 2.84 (d  $\frac{1}{2}$  AB q, 1H,  $J = 14.4, 6.3$  Hz, allylic CH<sub>2</sub>), 2.74

(dd, 1H,  $J = 12.9, 9.3$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.73-2.67 (m, 1H, allylic CH<sub>2</sub>), 2.66 (dd, 1H,  $J = 12.9, 2.2$  Hz, C(6) $\text{H}_{\text{endo}}$ ), 1.13 (t, 3H,  $J = 6.9$  Hz, Me);  $\delta$  199.3 (-C=O), 169.5 (-O-C=O), 132.4, 120.6, 103.3, 80.9, 79.9, 79.3, 73.7, 66.7, 51.8 (OMe), 51.6 (OMe), 39.71, 39.67, 15.1 (Me).

**Major isomer 239b:** colorless solid, mp 66-68 °C,  $^1\text{H}$  NMR  $\delta$  6.15-6.05 (m, 1H, olefinic), 5.18 (d, 1H,  $J = 8.8$  Hz, olefinic), 5.15 (d, 1H,  $J$



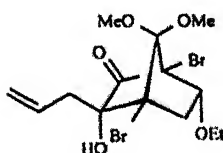
$= 16.3$  Hz, olefinic), 4.12 (dd, 1H,  $J = 9.8, 1.4$  Hz, C(5) $\text{H}_{\text{exo}}$ ), 3.69-3.64 (m, 1H, merged with OMe, -O-CH<sub>2</sub>), 3.67 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.50 (dq,

1H,  $J = 9.5, 7.1$  Hz, -O-CH<sub>2</sub>), 2.98 (dd, 1H,  $J = 13.7, 9.8$  Hz, C(6) $\text{H}_{\text{exo}}$ ), 2.68 (d  $\frac{1}{2}$  AB q, 1H,  $J = 14.6, 6.1$  Hz, allylic CH<sub>2</sub>), 2.57 (d  $\frac{1}{2}$  AB q, 1H,  $J = 14.6, 7.8$  Hz, allylic CH<sub>2</sub>), 2.26 (dd, 1H,  $J = 13.7, 1.2$  Hz, C(6) $\text{H}_{\text{endo}}$ ), 1.13 (t, 3H,  $J = 6.9$  Hz, Me);  $\delta$  200.1 (-C=O), 132.4, 118.7,

105.6, 81.3, 80.3 (carbinol C), 79.7, 72.4, 66.6, 52.3 (OMe), 51.8 (OMe), 39.4, 36.5, 15.1 (Me); IR (KBr) 3500, 2950, 1770, 1600, 1430  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{14}\text{H}_{20}\text{Cl}_2\text{O}_5$ : C 49.57, H 5.94; Found C 49.54, H 5.97.

**Acyloin 240b,241b:** Yield 94%, mixture of regioisomers (18:82).

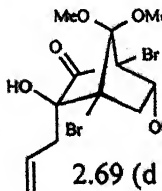
**Minor isomer 240b:** (sample recorded with enriched sample of minor isomer (88:22, 240b:241c),  $^1\text{H}$  NMR  $\delta$  6.28–6.18 (m, 1H, olefinic), 5.29 (d, 1H,  $J = 10.7$  Hz, olefinic), 5.24 (d, 1H,  $J = 17.6$  Hz, olefinic),



4.17 (dd, 1H,  $J = 9.0, 2.4$  Hz,  $\text{C}(5)\text{H}_{\text{exo}}$ ), 3.71 (s, 3H, OMe), 3.69–3.65 (m, 1H,  $-\text{O}-\text{CH}_2$ ), 3.62 (s, 3H, OMe), 3.58–3.53 (m, 1H,  $-\text{O}-\text{CH}_2$ ), 3.14 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.87–2.79 (m, 2H),

2.84 (d  $\frac{1}{2}$  AB q, 1H,  $J = 14.4, 6.3$  Hz, allylic  $\text{CH}_2$ ), 2.78 (dd, 1H,  $J = 13.1, 2.7$  Hz,  $\text{C}(6)\text{H}_{\text{endo}}$ ), 1.13 (t, 3H,  $J = 6.9$  Hz, Me);  $\delta$  198.6 ( $-\text{C}=\text{O}$ ), 132.4, 120.8, 103.3, 81.0, 79.4, 73.9, 66.1, 66.7, 51.9 (OMe), 51.6 (OMe), 41.9, 41.6, 15.1 (Me).

**Major isomer 241b:** colorless solid, mp 78–80  $^\circ\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  6.18–6.08 (m, 1H, olefinic), 5.17 (d, 1H,  $J = 9.8$  Hz, olefinic), 5.15 (d, 1H,  $J = 17.1$  Hz, olefinic), 4.19 (dd, 1H,  $J = 9.5, 1.7$  Hz,  $\text{C}(5)\text{H}_{\text{exo}}$ ), 3.71 (s,

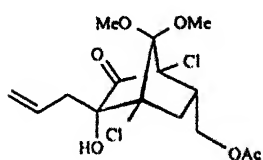


3H, OMe), 3.70–3.63 (m, 1H, merged with OMe,  $-\text{O}-\text{CH}_2$ ), 3.66 (s, 3H, OMe), 3.54 (dq, 1H,  $J = 9.3, 7.1$  Hz,  $-\text{O}-\text{CH}_2$ ), 2.90 (dd, 1H,  $J = 13.6, 9.8$  Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 2.69 (d  $\frac{1}{2}$  AB q, 1H,  $J = 14.4, 5.9$  Hz, allylic  $\text{CH}_2$ ), 2.55 (d  $\frac{1}{2}$  AB

q, 1H,  $J = 14.4, 7.8$  Hz, allylic  $\text{CH}_2$ ), 2.38 (dd, 1H,  $J = 13.6, 1.7$  Hz,  $\text{C}(6)\text{H}_{\text{endo}}$ ), 1.13 (t, 3H,  $J = 7.0$  Hz, Me);  $\delta$  199.1 ( $-\text{C}=\text{O}$ ), 132.5, 118.7, 105.7, 81.3, 80.2 (carbinol C), 74.3, 66.6, 66.4, 52.5 (OMe), 52.1 (OMe), 40.9, 36.8, 15.1 (Me); IR (KBr) 3300, 2950, 1770, 1100  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{14}\text{H}_{20}\text{Br}_2\text{O}_5$ : C 39.28, H 4.71; Found C 39.31, H 4.74.

**Acyloin 238c, 239c:** Yield 71%, mixture of regioisomers (77:23).

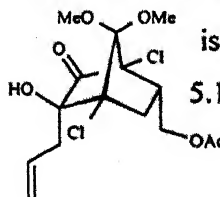
**Major isomer 238c:** colorless solid, mp 106–108 °C,  $^1\text{H}$  NMR  $\delta$  6.25–6.08 (m, 1H, olefinic), 5.39 (d, 1H,  $J = 10.2$  Hz, olefinic), 5.30 (d, 1H,  $J$



= 17.3 Hz, olefinic), 4.10 (d  $\frac{1}{2}$  AB q, 1H,  $J = 11.4, 5.5$  Hz,  $\text{CH}_2\text{-O-}$ ), 3.94 (d  $\frac{1}{2}$  AB q, 1H,  $J = 11.2, 8.5$  Hz,  $\text{CH}_2\text{-O-}$ ), 3.69 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.02 (s, 1H,  $\text{D}_2\text{O}$

exchangeable, OH), 2.87–2.80 (m, 2H), 2.70–2.64 (m, 1H, one of  $J = 13.9$  Hz), 2.60 (dd, 1H,  $J = 12.4, 4.4$  Hz,  $\text{C}(6)\text{H}_{\text{endo}}$ ), 2.51 (dd, 1H,  $J_1 = J_2 = 12.2$  Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 2.03 (s, 3H, Me);  $\delta$  203.7 ( $-\text{C}=\text{O}$ ), 170.6 ( $-\text{O}-\text{C}=\text{O}$ ), 131.8, 122.7, 103.3, 78.4 (carbinol C), 78.1, 73.6, 62.8, 51.8 (OMe), 51.6 (OMe), 42.2, 39.7, 34.6, 20.7 (Me); IR (KBr) 3300, 2900, 1760, 1690, 1600  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{15}\text{H}_{20}\text{Cl}_2\text{O}_6$ : C 49.06, H 5.49; Found C 49.01, H 5.52.

**Minor isomer 239c:** (sample recorded with enriched sample of minor isomer),  $^1\text{H}$  NMR  $\delta$  6.17–6.09 (m, 1H, olefinic), 5.23–

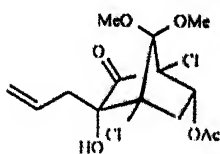


5.18 (m, 2H, olefinic), 4.15 (d  $\frac{1}{2}$  AB q, 1H,  $J = 12.2, 6.6$  Hz,  $\text{CH}_2\text{-O-}$ ), 4.00 (d  $\frac{1}{2}$  AB q, 1H,  $J = 12.0,$

4.2 Hz, CH<sub>2</sub>-O-), 3.71 (s, 3H, OMe), 3.66 (s, 3H, OMe), 2.91-2.85 (m, 1H, C(6)H<sub>exo</sub>), 2.74 (d ½ AB q, 1H,  $J = 14.9, 6.1$  Hz, allylic CH<sub>2</sub>), 2.67 (dd, 1H,  $J_1 = J_2 = 13.0$  Hz, C(6)H<sub>exo</sub>), 2.61 (d ½ AB q, 1H,  $J = 14.9, 8.2$  Hz, allylic CH<sub>2</sub>), 2.25 (dd, 1H,  $J = 13.1, 4.7$  Hz, C(6)H<sub>endo</sub>), 2.02 (s, 3H, Me);  $\delta$  202.7 (-C=O), 170.3 (-O-C=O), 131.2, 119.3, 105.3, 80.2 (carbinol C), 78.5, 72.5, 61.2, 51.5 (OMe), 52.0 (OMe), 41.1, 36.5, 34.2, 20.6 (Me).

**Acylolin 238d, 239d:** Yield 92%, mixture of regioisomers (23:77).

**Minor isomer 238d:** colorless crystals (dichloromethane-hexane), mp 125-126 °C, <sup>1</sup>H NMR  $\delta$  6.26-6.18 (m, 1H, olefinic), 5.42-5.37 (m, 2H,



olefinic), 5.32 (dd, 1H,  $J = 10.0, 2.7$  Hz, C(5)H<sub>exo</sub>), 3.69 (s, 3H, OMe), 3.61 (s, 3H, OMe), 2.89 (d ½ AB q, 1H,  $J = 13.9, 5.7$  Hz, allylic CH<sub>2</sub>), 2.95 (s, 1H, D<sub>2</sub>O exchangeable, OH), 2.84 (dd, 1H,  $J = 13.4, 10.0$  Hz, C(6)H<sub>exo</sub>), 2.74 (dd, 1H,  $J = 13.6, 2.7$  Hz, C(6)H<sub>endo</sub>), 2.69 (d ½ AB q, 1H,  $J = 14.1, 9.5$  Hz, allylic CH<sub>2</sub>), 2.04 (s, 3H, Me);  $\delta$  198.9 (-C=O), 169.5 (-O-C=O), 130.9, 119.4, 102.8, 80.2 (carbinol carbon), 74.9, 72.1, 65.7, 52.6 (OMe), 52.3 (OMe), 40.5, 37.1, 20.6 (Me). IR (KBr) 3350, 2900, 1740, 1710, 1610 cm<sup>-1</sup>; Anal. Calcd. for C<sub>14</sub>H<sub>18</sub>Cl<sub>2</sub>O<sub>6</sub>: C 47.61, H 5.14; Found C 47.67, H 5.20.

Irradiation of the olefinic proton at 6.26-6.18 (m, 1H, olefinic) carried out to assign the allylic CH<sub>2</sub>, C(6)H<sub>exo</sub> and C(6)H<sub>endo</sub> protons, which

resulted in the disappearance of the corresponding couplings in allylic  $\text{CH}_2$  proton.

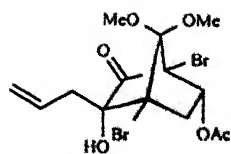
**Major isomer 239c:** colorless crystals (dichloromethane-hexane), mp 75-76 °C,  $^1\text{H}$  NMR  $\delta$  6.11-6.00 (m, 1H, olefinic), 5.36 (dd, 1H,  $J =$

10.3, 2.0 Hz,  $\text{C}(5)\text{H}_{\text{exo}}$ ), 5.18 (d, 1H,  $J = 10.0$  Hz, olefinic), 5.12 (d, 1H,  $J = 17.1$  Hz, olefinic), 3.67 (s, 3H, OMe), 3.61 (s, 3H, OMe), 2.98 (dd, 1H,  $J = 14.4$ , 10.3 Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 2.58 (d  $\frac{1}{2}$  AB q, 1H,  $J = 14.6$ , 6.4 Hz, allylic  $\text{CH}_2$ ), 2.44 (d  $\frac{1}{2}$  AB q, 1H,  $J = 14.6$ , 7.8 Hz, allylic  $\text{CH}_2$ ), 2.20 (dd, 1H,  $J = 14.4$ , 2.0 Hz,  $\text{C}(6)\text{H}_{\text{endo}}$ ), 2.07 (s, 3H, Me);  $\delta$  199.7 ( $-\text{C}=\text{O}$ ), 169.5 ( $-\text{O}-\text{C}=\text{O}$ ), 130.8, 119.3, 105.3, 80.1 (carbinol C), 79.2, 73.3, 52.4 (OMe), 52.2 (OMe), 39.0, 36.8, 20.7 (Me); IR (KBr) 3350, 2900, 1750, 1700, 1620, 1440  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{14}\text{H}_{11}\text{Cl}_2\text{O}_6$ : C 47.61, H 5.14.

**Acyloin 240d, 241d:** Yield 91%, mixture of regioisomers (25:77)

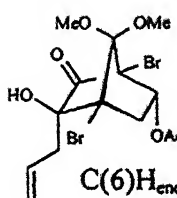
**Minor isomer 240d:** (sample recorded with enriched sample of minor isomer (88:22, 240d:241d),  $^1\text{H}$  NMR  $\delta$  6.27-6.14 (m, 1H, olefinic),

5.43-4.33 (m, 2H, olefinic), 5.35 (dd, 1H,  $J = 9.8$ , 2.7 Hz,  $\text{C}(5)\text{H}_{\text{exo}}$ ), 3.73 (s, 3H, OMe), 3.64 (s, 3H, OMe), 2.96 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.95 (d  $\frac{1}{2}$  AB q, 1H,  $J = 13.6$ , 9.9 Hz, allylic  $\text{CH}_2$ ), 2.90 (d  $\frac{1}{2}$  AB q, 1H,  $J = 13.6$ , 5.6 Hz, allylic  $\text{CH}_2$ ), 2.83 (dd, 1H,  $J = 13.4$ , 2.7 Hz,  $\text{C}(6)\text{H}_{\text{exo}}$ ), 2.65 (dd, 1H,  $J = 13.9$ , 9.8 Hz,  $\text{C}(6)\text{H}_{\text{endo}}$ ), 2.04



(s, 3H, Me);  $\delta$  198.8 (-C=O), 170.0 (-O-C=O), 131.7, 122.6, 102.9, 78.6, 74.4, 71.7, 66.3, 52.0 (OMe), 51.6 (OMe), 41.8, 40.7, 20.5 (Me).

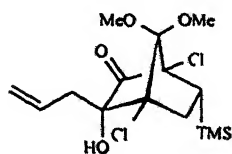
**Major isomer 241d:** colorless solid, mp 82-83 °C,  $^1\text{H}$  NMR  $\delta$  6.18-6.07 (m, 1H, olefinic), 5.44 (dd, 1H,  $J$  = 10.0, 5.4 Hz, C(5) $\text{H}_{\text{exo}}$ ), 5.22 (d, 1H,  $J$  = 10.0 Hz, olefinic), 5.15 (d, 1H,  $J$  = 17.1 Hz, olefinic), 3.74 (s, 3H, OMe), 3.69 (s, 3H, OMe), 3.09 (dd, 1H,  $J$  = 14.4, 10.0 Hz,

 C(6) $\text{H}_{\text{exo}}$ ), 2.61 (d  $\frac{1}{2}$  AB q, 1H,  $J$  = 14.6, 6.4 Hz, allylic  $\text{CH}_2$ ), 2.46 (d  $\frac{1}{2}$  AB q, 1H,  $J$  = 14.6, 7.8 Hz, allylic  $\text{CH}_2$ ), 2.30 (dd, 1H,  $J$  = 14.6, 2.0 Hz, C(6) $\text{H}_{\text{endo}}$ ), 2.05 (s, 3H, Me);  $\delta$  198.9 (-C=O), 169.5 (-O-C=O),

130.9, 119.4, 105.5, 80.0 (carbinol C), 74.9, 72.1, 65.7, 52.6 (OMe), 52.3 (OMe), 40.5, 37.0, 20.6 (Me); IR (KBr) 3350, 2900, 1740 (br), 1610, 1360  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{14}\text{H}_{18}\text{Br}_2\text{O}_6$ : C 38.04, H 4.10; Found C 38.10, H 4.13.

**Acyloin 238e, 239e:** Yield 91%, mixture of regioisomers (91:9).

**Major isomer 238e:** colorless crystals (hexane), mp 107-108 °C,  $^1\text{H}$  NMR  $\delta$  6.21-6.11 (m, 1H, olefinic), 5.36 (d, 1H,  $J$  = 10.0 Hz, olefinic),

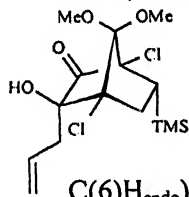


5.30 (d, 1H,  $J$  = 16.8 Hz, olefinic), 3.66 (s, 3H, OMe), 3.57 (s, 3H, OMe), 2.84 (d  $\frac{1}{2}$  AB q, 1H,  $J$  = 13.5, 5.6 Hz, allylic  $\text{CH}_2$ ), 2.83 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.62 (dd, 1H,  $J$  = 12.5, 6.1 Hz, C(5) $\text{H}_{\text{exo}}$ ), 2.61 (d  $\frac{1}{2}$  AB q,  $J$  = 13.6, 9.3 Hz, allylic  $\text{CH}_2$ ), 2.35 (dd, 1H,  $J$  = 13.1, 12.5 Hz, C(6) $\text{H}_{\text{exo}}$ ), 1.91 (dd, 1H,  $J$  = 13.1, 6.0 Hz,

C(6)H<sub>endo</sub>). 0.00 (s, 9H, Me);  $\delta$  203.7 (-C=O), 131.9, 122.7, 103.3, 79.0, 78.2 (carbinol C), 74.0, 51.6 (OMe), 51.4 (OMe), 39.7, 33.1, 30.9, -1.7 (SiMe<sub>3</sub>); IR (KBr) 3480, 2950, 1780, 1620 cm<sup>-1</sup>; Anal. Calcd. for C<sub>15</sub>H<sub>24</sub>SiCl<sub>2</sub>O<sub>4</sub>: C 49.05, H 6.59; Found C 49.10, H 6.62.

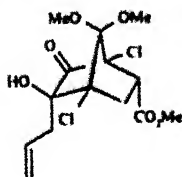
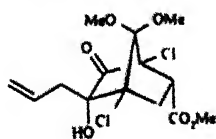
Irradiation of the olefinic proton at 6.22-6.13 (m, 1H, olefinic) carried out to assign the allylic CH<sub>2</sub> and C(6)H<sub>exo</sub> protons. Two protons, one of the allylic CH<sub>2</sub> and C(6)H<sub>exo</sub> protons appeared as a multiplet. After irradiation, the coupling constant  $J = 5.6$  was disappeared from one of the allylic CH<sub>2</sub> proton 2.84 (d ½ AB q, 1H,  $J = 13.5, 5.6$  Hz, allylic CH<sub>2</sub>).

**Minor isomer 239e:** colorless solid, mp 108-110 °C, <sup>1</sup>H NMR  $\delta$  6.11-6.01 (m, 1H, olefinic), 5.14 (d, 1H,  $J = 9.5$  Hz, olefinic), 5.11 (d, 1H,  $J = 15.6$  Hz, olefinic), 3.64 (s, 3H, OMe), 3.57 (s, 3H, OMe), 2.52 (dd, 1H,  $J = 15.3, 6.1$  Hz, C(5)H<sub>exo</sub>), 2.48 (d ½ AB q, 1H,  $J = 14.6, 9.5$  Hz, allylic CH<sub>2</sub>), 2.39 (d ½ AB q,  $J = 14.6, 7.8$  Hz, allylic CH<sub>2</sub>), 2.06-2.00 (m, 2H, C(6)H<sub>exo</sub>, C(6)H<sub>endo</sub>), 0.00 (s, 9H, Me);  $\delta$  203.8 (-C=O), 131.2, 119.1, 103.3, 79.9, 72.4, 52.4 (OMe), 51.9 (OMe), 36.2, 33.4, 29.8, 0.995 (SiMe<sub>3</sub>); IR (KBr) 3500, 2950, 1770, 1610, 1260 cm<sup>-1</sup>.



**Acyloin 238f, 239f:** Yield 92%, inseparable mixture of regioisomers (43:57); obtained as a viscous liquid, <sup>1</sup>H NMR (from the mixture)  $\delta$  6.30-6.20 (m, 1H, olefinic, minor isomer), 6.15-6.05 (m, 1H, olefinic, major isomer), 5.24-5.17 (m, 4H, olefinic), 3.73 (s, 3H, OMe), 3.72 (s,

3H, OMe), 3.71 (s, 6H, OMe), 3.65 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.46 (dd, 1H,  $J = 12.7, 4.4$  Hz, C(5)H<sub>exo</sub>, major isomer), 3.42 (dd, 1H,  $J$



= 12.2, 3.9 Hz, C(5)H<sub>exo</sub>, minor isomer), 2.83-2.71 (m, 5H), 2.65 (dd, 1H,  $J_1 = J_2 = 12.7$  Hz, C(6)H<sub>exo</sub>), 2.60 (dd, 1H,  $J = 13.9,$

7.9 Hz, allylic CH<sub>2</sub>, minor isomer), 2.50 (dd, 1H,  $J = 13.6, 4.3$  Hz, C(6)H<sub>endo</sub>, major isomer).

Irradiation experiment of vinylic hydrogen and C(5)H<sub>exo</sub> proton of both *endo* and *exo* isomer was carried out to assign the protons.

<sup>13</sup>C NMR (Major isomer, from the mixture):  $\delta$  201.0 (-C=O), 170.8 (-O-C=O), 131.1, 119.2, 105.1, 80.2 (carbinol C), 77.8, 72.0, 52.8 (OMe), 52.3 (OMe), 51.9 (OMe), 46.7, 36.4, 34.3.

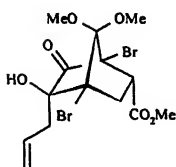
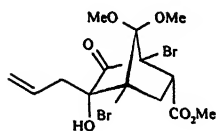
<sup>13</sup>C NMR (Minor isomer, from the mixture):  $\delta$  199.9 (-C=O), 172.9 (-O-C=O), 132.6, 119.3, 103.2, 79.4 (carbinol C), 77.9, 73.6, 53.2 (OMe), 51.8 (OMe), 51.6 (OMe), 47.7, 39.9, 34.4.

IR (KBr) 3300, 2900, 1760-1700 (br), 1620 cm<sup>-1</sup>; Anal. Calcd for C<sub>14</sub>H<sub>18</sub>Cl<sub>2</sub>O<sub>6</sub>: C 47.61, H 5.14; Found C 47.66, H 5.17.

**Acyloin 240f,241f:** Yield 94%, inseparable mixture of regioisomers (45:55); obtained as a viscous liquid, <sup>1</sup>H NMR (from the mixture)  $\delta$  6.22-6.13 (m, 1H, olefinic, minor isomer), 6.11-6.01 (m, 1H, olefinic, major isomer), 5.17-5.06 (m, 4H, olefinic), 3.674 (s, 6H, OMe), 3.667 (s, 3H, OMe), 3.66 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.59 (s, 3H,



OMe), 3.44 (dd, 1H,  $J = 12.7, 4.4$  Hz, C(5)H<sub>exo</sub>, major isomer), 3.39 (dd, 1H,  $J = 12.0, 4.1$  Hz, C(5)H<sub>exo</sub>, minor isomer), 2.86-2.79 (m, 2H),



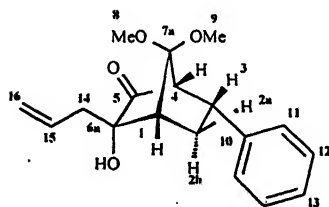
2.76-2.65 (m, 4H), 2.53-2.46 (m, 1H), 2.47 (dd, 1H,  $J = 13.4, 4.3$  Hz, C(6)H<sub>endo</sub>, major isomer).

<sup>13</sup>C NMR (Major isomer, from the mixture):  $\delta$  200.3 (-C=O), 171.0 (-O-C=O), 131.2, 119.5, 105.3, 80.1 (carbinol C), 70.7, 65.5, 52.8 (OMe), 52.6 (OMe), 52.0 (OMe), 48.4, 36.8, 36.2.

<sup>13</sup>C NMR (Minor isomer, from the mixture):  $\delta$  199.3 (-C=O), 172.9 (-O-C=O), 132.8, 119.3, 103.4, 79.6 (carbinol C), 70.9, 66.9, 53.2 (OMe), 51.9 (OMe), 51.8 (OMe), 49.2, 42.1, 36.5.

IR (KBr) 3400, 2900, 1740 (br), 1620. 1400 cm<sup>-1</sup>; Anal. Calcd for C<sub>14</sub>H<sub>18</sub>Br<sub>2</sub>O<sub>6</sub>: C 38.04, H 4.10; Found C 38.10, H 4.07.

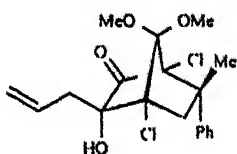
**Acylolin 242:** Procedure is similar to that adopted for the bridgehead reduction of lactones (Chapter 1A, page no. 194); Yield 95%, colorless



solid, mp 104-106 °C, <sup>1</sup>H NMR  $\delta$  7.34 (m, 2H, aromatic), 7.28-7.24 (m, 2H, aromatic), 7.18-7.14 (m, 1H, aromatic), 6.02-5.92 (m, 1H, olefinic), 5.24 (d, 1H,  $J = 10.5$  Hz, olefinic), 5.20 (d, 1H,  $J = 17.3$  Hz, olefinic), 3.78 (dt, 1H,  $J = 11.2, 5.2$  Hz, C(3)H<sub>exo</sub>), 3.39 (s, 3H, C(9)OMe), 3.29 (s, 3H, C(8)OMe), 3.03 (dd, 1H,  $J = 5.1, 1.9$  Hz, C(4)H),

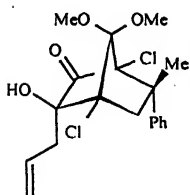
2.71-2.66 (m, 1H, allylic CH<sub>2</sub>, C(1)H), 2.63-2.57 (m, 1H, allylic CH<sub>2</sub>, merged with C(2)H<sub>b</sub>), 2.57 (dd, 1H,  $J = 12.7, 4.8$  Hz, C(2)H<sub>b</sub>), 2.29 (ddd, 1H,  $J = 12.7, 11.2, 4.6$  Hz, C(2)H<sub>b</sub>), 2.24 (s, 1H, D<sub>2</sub>O exchangeable, OH);  $\delta$  212.4 (C<sub>3</sub>), 140.5 (C<sub>10</sub>), 132.9 (C<sub>11</sub>), 128.2 (CH), 128.0 (CH), 126.4 (CH), 120.3 (CH<sub>2</sub>, C<sub>16</sub>), 109.1 (C<sub>7a</sub>), 78.5 (carbinol C), 59.6 (CH), 51.0 (Me), 49.7 (Me), 46.7 (CH), 42.1 (CH<sub>2</sub>), 41.2 (CH, C<sub>1</sub>), 25.5 (CH<sub>2</sub>); IR (KBr) 3500, 2950, 1770, 1620, 1260 cm<sup>-1</sup>; Anal. Calcd. for C<sub>18</sub>H<sub>22</sub>O<sub>4</sub>: C 71.50, H 7.33 ; Found C 71.56, H 7.37.

**Acyloin 243:** Colorless solid (contaminated with the undetected isomer), mp 86-90 °C, <sup>1</sup>H NMR  $\delta$  7.46-7.44 (m, 2H, aromatic), 7.28-7.21 (m, 2H, aromatic), 7.16-7.12 (m, 1H, aromatic), 6.18-6.13 (m, 1H,



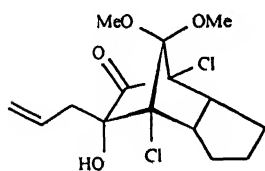
olefinic), 5.24 (d, 1H,  $J = 10.0$  Hz, olefinic), 5.19 (d, 1H,  $J = 17.1$  Hz, olefinic), 3.75 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.58 (d, 1H,  $J = 12.0$  Hz), 2.77 (d ½ AB q,  $J = 13.7, 6.1$  Hz, allylic CH<sub>2</sub>), 2.68 (d, 1H,  $J = 12.0$  Hz), 2.60 (d ½ AB q,  $J = 13.7, 9.3$  Hz, allylic CH<sub>2</sub>), 2.42 (s, 1H, D<sub>2</sub>O exchangeable, OH), 1.64 (s, 3H, Me);  $\delta$  200.7 (-C=O), 145.1, 132.2, 128.0, 126.4, 126.3, 122.3, 103.6, 84.2, 77.7 (carbinol C), 73.7, 51.7 (OMe), 51.5 (OMe), 46.7, 45.4, 40.0, 27.4.

**Acyloin 244:** Colorless crystals (dichloromethane-hexane, 1:2), mp 103-105 °C,  $^1\text{H}$  NMR  $\delta$  7.31-7.28 (m, 2H, aromatic), 7.22-7.19 (m, 2H, aromatic), 7.13-7.10 (m, 1H, aromatic), 5.72-5.62 (m, 1H, olefinic), 4.88 (d, 1H,  $J = 10.2$  Hz, olefinic), 4.45 (d, 1H,  $J = 17.1$  Hz, olefinic), 3.67 (s, 3H, OMe), 3.59 (s, 3H, OMe), 3.31 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.95 (d, 1H,  $J = 13.0$  Hz), 2.83 (d, 1H,  $J = 13.0$  Hz), 1.89 (d  $\frac{1}{2}$  AB q,  $J = 14.4$ , 7.3 Hz, allylic  $\text{CH}_2$ ), 1.71 (d  $\frac{1}{2}$  AB q,  $J = 14.4$ , 6.8 Hz, allylic  $\text{CH}_2$ ), 1.58 (s, 3H, Me);  $\delta$  202.3 ( $\text{-C=O}$ ), 130.7, 128.7, 126.9, 126.2, 119.1, 105.6, 84.5 (carbinol C), 80.0, 73.0, 52.2 (OMe), 51.7 (OMe), 47.1, 46.3, 36.8, 32.1; IR (KBr) 3500, 2950, 1770, 1620, 1200  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{19}\text{H}_{22}\text{Cl}_2\text{O}_4$ : C 59.23, H 5.76; Found C 59.27, H 5.79.



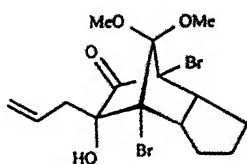
### Disubstituted Acyloins:

**Acyloin 246i:** Yield 96%, colorless solid, mp 70-72 °C,  $^1\text{H}$  NMR  $\delta$  6.11-6.00 (m, 1H, olefinic), 5.37 (d, 1H,  $J = 9.8$  Hz, olefinic), 5.29 (d, 1H,  $J = 17.1$  Hz, olefinic), 3.64 (s, 3H, OMe), 3.55 (s, 3H, OMe), 3.46-3.40 (m, 1H), 2.99 (dd, 1H,  $J = 13.6$ , 5.4 Hz, allylic  $\text{CH}_2$ ), 2.90 (ddd, 1H,  $J_1 = J_2 = 12.0$  Hz,  $J_3 = 7.4$  Hz), 2.83 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.68 (dd, 1H,  $J = 13.6$ , 9.8 Hz, allylic  $\text{CH}_2$ ), 2.56-2.47 (m, 1H), 1.91-1.80 (m, 1H), 1.73-1.65 (m, 1H), 1.61-1.46 (m, 2H), 1.39-1.30 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  204.0 ( $\text{-C=O}$ ), 131.5,



123.2, 106.0, 81.0 (carbinol C), 78.9, 74.9, 52.9, 51.7, 51.1, 47.8, 41.6, 26.7, 25.8, 25.1; IR (KBr) 3400, 2900, 1740, 1600, 1420  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{15}\text{H}_{20}\text{Cl}_2\text{O}_4$ : C 53.74, H 6.01; Found C 53.80, H 6.04.

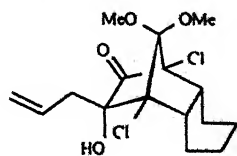
**Acyloin 247i:** Yield 98%, colorless solid, mp 72-74 °C,  $^1\text{H}$  NMR  $\delta$  6.12-6.02 (m, 1H, olefinic), 5.41 (d, 1H,  $J = 10.0$  Hz, olefinic), 5.32 (d, 1H,  $J = 17.0$  Hz, olefinic), 3.72 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.61-



3.54 (m, 1H), 3.08-3.02 (m, 1H), 3.01-2.96 (m, 1H), 2.90 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.66 (dd, 1H,  $J = 13.6, 10.3$  Hz, allylic  $\text{CH}_2$ ), 2.53 (ddd, 1H,  $J_1 = J_2 = 12.4$  Hz,  $J_3 = 5.9$  Hz), 1.88-

1.71 (m, 2H), 1.66-1.49 (m, 2H), 1.43-1.33 (m, 1H), 1.39-1.30 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  203.4 ( $-\text{C}=\text{O}$ ), 131.5, 123.2, 106.1, 81.3 (carbinol C), 72.6, 69.3, 54.8, 51.8, 51.3, 50.9, 43.6, 26.2, 26.1, 25.5; IR (KBr) 3400, 2900, 1750, 1610, 1400  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{15}\text{H}_{20}\text{Br}_2\text{O}_4$ : C 42.48, H 5.46; Found C 42.52, H 5.49.

**Acyloin 246j:** Yield 96%, colorless solid, mp 108-110 °C,  $^1\text{H}$  NMR  $\delta$

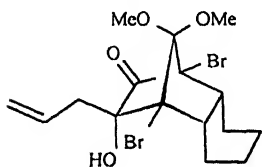


6.19-6.09 (m, 1H, olefinic), 5.39 (d, 1H,  $J = 10.0$  Hz, olefinic), 5.31 (d, 1H,  $J = 17.1$  Hz, olefinic), 3.67 (s, 3H, OMe), 3.58 (s, 3H, OMe), 3.10-3.03 (m, 1H, one of the  $J = 11.2$

Hz), 2.94 (dd, 1H,  $J = 13.8, 5.4$  Hz, allylic  $\text{CH}_2$ ), 2.90 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.70 (dd, 1H,  $J = 13.7, 9.8$  Hz, allylic  $\text{CH}_2$ ), 2.50

(ddd, 1H,  $J = 13.3, 12.8, 4.4$  Hz), 2.30 (ddd, 1H,  $J_1 = J_2 = 11.2$  Hz,  $J_3 = 5.7$  Hz), 1.68-1.54 (m, 4H), 1.35-1.22 (m, 2H), 1.14-1.03 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  203.2 (C=O), 131.7, 122.9, 103.5, 81.0 (carbinol C), 80.2, 76.6, 51.8 (OMe), 51.4 (OMe), 45.1, 42.3, 41.5, 20.6, 20.3, 19.6, 18.8; IR (KBr) 3400, 2900, 1760, 1620, 1080  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{16}\text{H}_{22}\text{Cl}_2\text{O}_4$ : C 55.02, H 6.35; Found C 55.08, H 6.38.

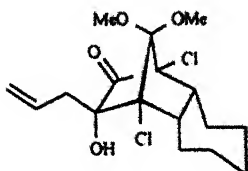
**Acylain 247j:** Yield 97%, colorless solid, mp 112-114°C,  $^1\text{H}$  NMR  $\delta$  6.18-6.08 (m, 1H, olefinic), 5.40 (d, 1H,  $J = 10.0$  Hz, olefinic), 5.32 (d,



1H,  $J = 17.1$  Hz, olefinic), 3.75 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.13 (ddd, 1H,  $J_1 = J_2 = 11.2$  Hz,  $J_3 = 7.2$  Hz), 2.97 (dd, 1H,  $J = 13.7, 5.6$  Hz, allylic  $\text{CH}_2$ ), 2.93 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.66 (dd, 1H,  $J = 13.7, 10.0$  Hz, allylic  $\text{CH}_2$ ), 2.53 (ddd, 1H,  $J_1 = J_2 = 13.7$  Hz,  $J_3 = 4.6$  Hz), 2.30 (ddd, 1H,  $J_1 = J_2 = 11.2$  Hz,  $J_3 = 5.1$  Hz), 1.72-1.55 (m, 4H), 1.45-1.33 (m, 1H), 1.24-1.17 (m, 1H), 1.14-1.13 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  202.6 (C=O), 131.8, 123.0, 103.4, 81.3 (carbinol C), 74.4, 71.6, 52.0 (OMe), 51.6 (OMe), 47.4, 43.8, 43.7, 20.7, 20.3, 19.9, 19.4; IR (KBr) 3400, 2950, 1760, 1620, 1360  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{16}\text{H}_{22}\text{Br}_2\text{O}_4$ : C 43.86, H 5.06; Found C 43.90, H 5.01.

**Acylain 246k:** Yield 96%, obtained as a viscous liquid,  $^1\text{H}$  NMR  $\delta$  6.16-6.06 (m, 1H, olefinic), 5.38 (d, 1H,  $J = 10.0$  Hz, olefinic), 5.31 (d, 1H,  $J = 17.1$  Hz, olefinic), 3.70 (s, 3H, OMe), 3.58 (s, 3H, OMe),

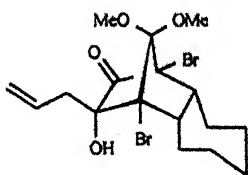
3.12 (dt, 1H,  $J = 12.5, 3.6$  Hz), 2.94 (dd, 1H,  $J = 13.8, 5.7$  Hz, allylic  $\text{CH}_2$ ), 2.87 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.68 (dd, 1H,  $J = 13.9, 9.6$



Hz, allylic  $\text{CH}_2$ ), 2.50 (dd, 1H,  $J_1 = J_2 = 12.4$  Hz), 2.26-2.17 (m, 1H), 2.01-1.89 (m, 3H), 1.80-1.78 (m, 1H), 1.68-1.63 (m, 1H), 1.22-1.08 (m, 3H), 1.00-0.95 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$

202.9 ( $-\text{C}=\text{O}$ ), 131.7, 123.0, 103.1, 81.4 (carbinol C), 80.2, 77.0, 51.8, 51.4, 50.7, 48.7, 41.6, 31.0, 30.7, 28.8, 25.5, 24.5; IR (KBr) 3400, 2900, 1760, 1620, 1380  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{17}\text{H}_{24}\text{Cl}_2\text{O}_4$ : C 56.21, H 6.66; Found C 56.24, H 6.69.

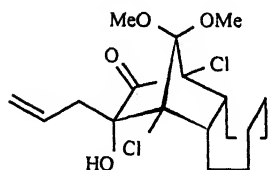
**Acylolin 247k:** Yield 97%, colorless solid, mp 93-195  $^\circ\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  6.15-6.05 (m, 1H, olefinic), 5.38 (d, 1H,  $J = 9.8$  Hz, olefinic), 5.31 (d, 1H,  $J = 17.1$  Hz, olefinic), 3.75 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.12



(dt, 1H,  $J = 12.5, 3.5$  Hz), 2.96 (dd, 1H,  $J = 13.9, 5.6$  Hz, allylic  $\text{CH}_2$ ), 2.90 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.53 (dd, 1H,  $J = 13.9, 9.8$  Hz, allylic  $\text{CH}_2$ ), 2.54 (dd, 1H,  $J_1 = J_2 =$

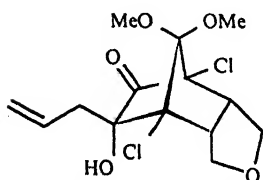
12.1 Hz), 2.24-2.15 (m, 1H), 2.04-1.97 (m, 3H), 1.77-1.67 (m, 2H), 1.21-1.08 (m, 3H), 0.99-0.90 (m, 1H);  $^{13}\text{C}$  NMR  $\delta$  202.3 ( $-\text{C}=\text{O}$ ), 131.7, 122.9, 102.1, 81.5 (carbinol C), 75.2, 72.5, 52.2, 52.1, 51.4, 49.5, 43.6, 30.8, 30.6, 29.1, 26.2, 25.0; IR (KBr) 3400, 2900, 1740, 1600, 1100  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{17}\text{H}_{24}\text{Br}_2\text{O}_4$ : C 45.16, H 5.35; Found C 45.21, H 5.31.

**Acyloin 246l:** Yield 98%, colorless solid, mp 82-84 °C,  $^1\text{H}$  NMR  $\delta$  6.17-6.06 (m, 1H, olefinic), 5.36 (d, 1H,  $J = 9.8$  Hz, olefinic), 5.29 (d,



1H,  $J = 17.1$  Hz, olefinic), 3.71 (s, 3H, OMe), 3.58 (s, 3H, OMe), 2.87 (dd, 1H,  $J = 13.9, 5.6$  Hz, allylic  $\text{CH}_2$ ), 2.82 (dd, 1H,  $J_1 = J_2 = 11.2$  Hz), 2.75 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.65 (dd, 1H,  $J = 13.9, 9.5$  Hz, allylic  $\text{CH}_2$ ), 2.51 (dd, 1H,  $J_1 = J_2 = 11.2$  Hz), 2.05-1.94 (m, 1H), 1.84-1.72 (m, 4H), 1.62-1.48 (m, 2H), 1.40-1.07 (5H);  $^{13}\text{C}$  NMR  $\delta$  202.6 ( $-\text{C}=\text{O}$ ), 131.8, 122.7, 102.7, 80.8 (2C), 77.9, 51.9 (OMe), 51.4 (OMe), 49.1, 48.7, 41.3, 31.6, 30.8, 25.7, 25.0, 23.8, 21.1; IR (KBr) 3300, 2800, 1740, 1600, 1420  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{18}\text{H}_{26}\text{Cl}_2\text{O}_4$ : C 57.30, H 5.87; Found C 57.35, H 5.91.

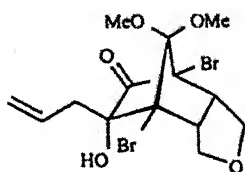
**Acyloin 246t:** Yield 95%, colorless solid, mp 84-86 °C,  $^1\text{H}$  NMR  $\delta$  6.17-6.06 (m, 1H, olefinic), 5.13 (d, 1H,  $J = 10.0$  Hz, olefinic), 5.09 (d,



1H,  $J = 17.1$  Hz, olefinic), 4.97 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 4.52 (d, 1H,  $J = 10.7$  Hz), 3.83 (d, 1H,  $J = 11.0$  Hz), 3.68 (s, 3H, OMe), 3.62 (s, 3H, OMe), 3.62-3.50 (m, 2H), 3.38 (dd, 1H,  $J = 10.7, 6.6$  Hz), 3.21 (ddd, 1H,  $J_1 = J_2 = 8.8$  Hz,  $J_3 = 2.0$  Hz), 2H);  $^{13}\text{C}$  NMR  $\delta$  202.9 ( $-\text{C}=\text{O}$ ), 132.7, 117.8, 105.2, 82.4, 76.9, 73.6, 67.1, 66.8, 53.0, 51.9 (OMe), 51.2 (OMe),

49.2, 41.1; IR (KBr) 3200, 2850, 1750, 1600, 1400  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{14}\text{H}_{18}\text{Cl}_2\text{O}_5$ : C 49.87, H 5.38; Found C 49.82, H 5.41.

**Acyloin 247t:** Yield 95%, colorless solid, mp 76 °C,  $^1\text{H}$  NMR  $\delta$  6.08-5.98 (m, 1H, olefinic), 5.07 (d, 1H,  $J = 10.0$  Hz, olefinic), 5.09 (d, 1H,  $J$



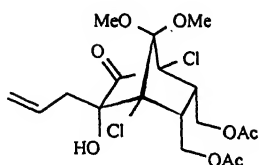
= 17.3 Hz, olefinic), 4.85 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 4.46 (d, 1H,  $J = 10.7$  Hz), 3.75 (d, 1H,  $J = 10.2$  Hz), 3.66 (s, 3H, OMe), 3.64 (dd, 1H,  $J = 10.5, 6.4$  Hz), 3.60 (s, 3H,

OMe), 3.54 (dd, 1H,  $J = 10.8, 7.3$  Hz), 3.32 (dd, 1H,  $J = 10.7, 6.7$  Hz), 3.27 (ddd, 1H,  $J_1 = J_2 = 9.7$  Hz,  $J_3 = 2.0$  Hz), 2.78-2.66 (m, 2H);  $^{13}\text{C}$  NMR  $\delta$  202.3 ( $\text{-C=O}$ ), 132.7, 117.9, 105.4, 82.6 (carbinol C), 70.0, 67.4, 67.3, 67.1, 54.8, 52.0, 51.3, 50.5, 43.2; IR (KBr) 3400, 2800, 1740, 1620, 1250  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{14}\text{H}_{18}\text{Br}_2\text{O}_5$ : C 39.46, H 4.26; Found C 39.41, H 4.29.

**Acyloin 246v:** Yield 98%, colorless solid (dichloromethane-hexane), mp 139-140 °C,  $^1\text{H}$  NMR  $\delta$  6.17-6.06 (m, 1H, olefinic), 5.40 (d, 1H,  $J = 9.3$  Hz, olefinic), 5.31 (d, 1H,  $J = 17.1$  Hz, olefinic), 4.50-4.40 (m, 2H), 4.21-4.11 (m, 2H), 3.73 (s, 3H, OMe), 3.61 (s, 3H, OMe), 3.33 (ddd, 1H,  $J_1 = J_2 = 10.1$  Hz,  $J_3 = 2.2$  Hz), 3.07-3.01 (m, 1H), 3.06 (s, 1H,  $\text{D}_2\text{O}$  exchangeable, OH), 2.84 (dd, 1H,  $J = 13.6, 5.6$  Hz, allylic  $\text{CH}_2$ ), 2.64 (dd, 1H,  $J = 13.9, 9.3$  Hz, allylic  $\text{CH}_2$ ), 2.06 (s, 3H, Me), 1.99 (s, 3H,

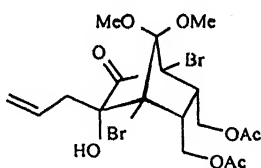


Me);  $^{13}\text{C}$  NMR  $\delta$  201.1 ( $-\text{C}=\text{O}$ ), 170.6 ( $\text{O}-\text{C}=\text{O}$ ), 170.2 ( $\text{O}-\text{C}=\text{O}$ ), 131.3, 123.4, 102.3, 80.0 (carbinol C), 77.6, 76.7, 61.1, 59.9, 52.1 (OMe), 51.8 (OMe), 46.9, 43.1, 40.4, 21.0 (Me), 20.6 (Me); IR (KBr) 3500, 2950,



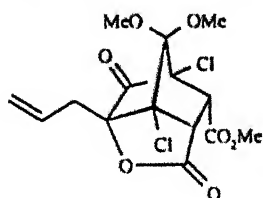
1760(br), 1600, 1380  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{18}\text{H}_{24}\text{Cl}_2\text{O}_8$ : C 49.22, H 5.51; Found C 49.26, H 5.49.

**Acylolin 247v:** Yield 99%, colorless solid (dichloromethane-hexane), mp 143-144  $^{\circ}\text{C}$ ,  $^1\text{H}$  NMR  $\delta$  6.20-6.09 (m, 1H, olefinic), 5.41 (d, 1H,  $J = 10.0$  Hz, olefinic), 5.32 (d, 1H,  $J = 17.1$  Hz, olefinic), 4.48 (d, 1H,  $J = 5.4$  Hz), 4.17 (d, 1H,  $J = 6.6$  Hz), 3.78 (s, 3H, OMe), 3.65 (s, 3H, OMe), 3.39 (ddd, 1H,  $J_1 = J_2 = 11.6$  Hz,  $J_3 = 5.6$  Hz), 3.08 (s, 1H,  $\text{D}_2\text{O}$



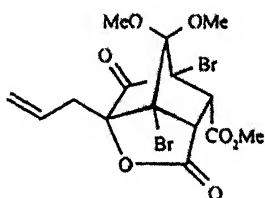
exchangeable, OH), 3.05 (ddd, 1H,  $J_1 = J_2 = 11.7$  Hz,  $J_3 = 6.5$  Hz), 2.84 (dd, 1H,  $J = 13.7, 5.6$  Hz, allylic  $\text{CH}_2$ ), 2.60 (dd, 1H,  $J = 13.9, 9.8$  Hz, allylic  $\text{CH}_2$ ), 2.06 (s, 3H, Me), 1.99 (s, 3H, Me);  $^{13}\text{C}$  NMR  $\delta$  200.7 ( $-\text{C}=\text{O}$ ), 170.6 ( $\text{O}-\text{C}=\text{O}$ ), 170.2 ( $\text{O}-\text{C}=\text{O}$ ), 131.4, 123.4, 102.2, 80.1 (carbinol C), 71.3, 71.2, 61.9, 60.3, 52.3 (OMe), 51.9 (OMe), 48.3, 44.0, 42.6, 21.0 (Me), 20.6 (Me); IR (KBr) 3350, 2900, 1730, 1610, 1320  $\text{cm}^{-1}$ ; Anal. Calcd. for  $\text{C}_{18}\text{H}_{24}\text{Br}_2\text{O}_8$ : C 40.93, H 4.58; Found C 40.97, H 4.55.

**Keto lactone 248:** Yield 97%, colorless solid (dichloromethane-hexane), mp 142-143 °C,  $^1\text{H}$  NMR  $\delta$  6.20-6.10 (m, 1H, olefinic), 5.26-5.21 (m, 2H, olefinic), 3.87 (d, 1H,  $J = 11.0$  Hz), 3.79 (s, 3H, OMe),



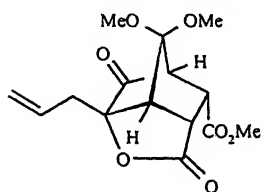
3.71 (s, 3H, OMe), 3.63 (s, 3H, OMe), 3.49 (d, 1H,  $J = 11.0$  Hz), 2.81 (AB q, 2H,  $J = 7.1, 1.3$  Hz, allylic  $\text{CH}_2$ );  $^{13}\text{C}$  NMR  $\delta$  191.9 ( $-\text{C}=\text{O}$ ), 170.6 ( $\text{O}-\text{C}=\text{O}$ ), 166.9 ( $\text{O}-\text{C}=\text{O}$ ), 129.8, 119.7, 101.5, 87.5, 76.3, 75.7, 53.4, 52.4, 52.1, 52.0, 50.6, 34.8; IR 2900, 1800-1750 (br), 1610, 1420  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{15}\text{H}_{16}\text{Cl}_2\text{O}_7$ : C 47.51, H 4.25; Found C 47.54, H 4.23.

**Keto lactone 249:** Yield 95%, colorless solid (dichloromethane-hexane), mp 140-142 °C,  $^1\text{H}$  NMR  $\delta$  6.22-6.11 (m, 1H, olefinic), 5.26-5.20 (m, 2H, olefinic), 3.88 (d, 1H,  $J = 10.9$  Hz), 3.75 (s, 3H, OMe),



3.72 (s, 3H, OMe), 3.67 (s, 3H, OMe), 3.56 (d, 1H,  $J = 10.9$  Hz), 2.84 (dt  $\frac{1}{2}$  AB q, 1H,  $J = 7.1, 1.3$  Hz, allylic  $\text{CH}_2$ ), 2.75 (dt  $\frac{1}{2}$  AB q, 1H,  $J = 7.1, 1.3$  Hz, allylic  $\text{CH}_2$ );  $^{13}\text{C}$  NMR  $\delta$  190.5 ( $-\text{C}=\text{O}$ ), 170.8 ( $\text{O}-\text{C}=\text{O}$ ), 167.0 ( $\text{O}-\text{C}=\text{O}$ ), 130.1, 119.5, 101.7, 87.5, 68.7, 67.2, 54.1, 53.3, 52.5, 52.2, 51.8, 37.0; IR 2900, 1760-1710 (br), 1600, 1440  $\text{cm}^{-1}$ ; Anal. Calcd for  $\text{C}_{15}\text{H}_{16}\text{Br}_2\text{O}_7$ : C 38.49, H 3.45; Found C 38.51, H 3.47.

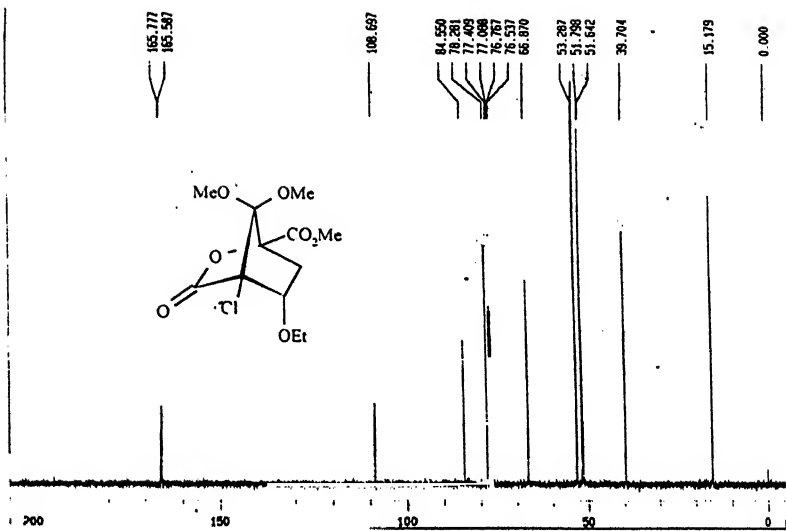
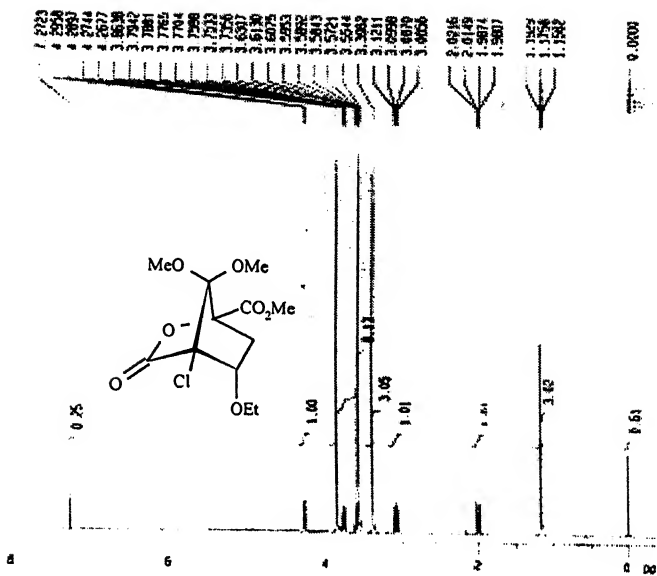
**Keto lactone 250:** Yield 95%, colorless solid, mp 98 °C, 5.90-5.80 (m, 1H, olefinic), 5.26-5.21 (m, 2H, olefinic), 3.70 (s, 3H, OMe), 3.62 (dd, 1H,  $J = 10.2, 3.7$  Hz), 3.40 (dd, 1H,  $J = 5.5, 1.1$  Hz), 3.32 (s, 3H, OMe), 3.30 (s, 3H, OMe), 3.27 (dd, 1H,  $J = 10.2, 5.1$ Hz), 3.08 (dd, 1H,



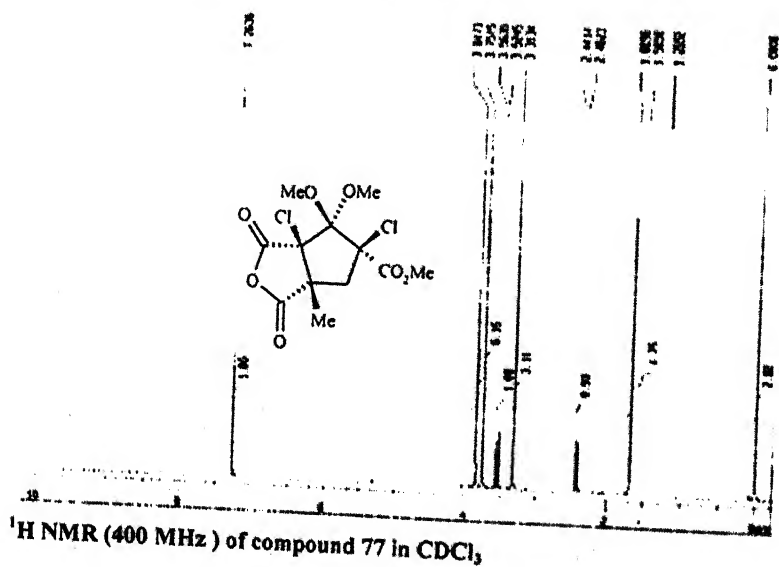
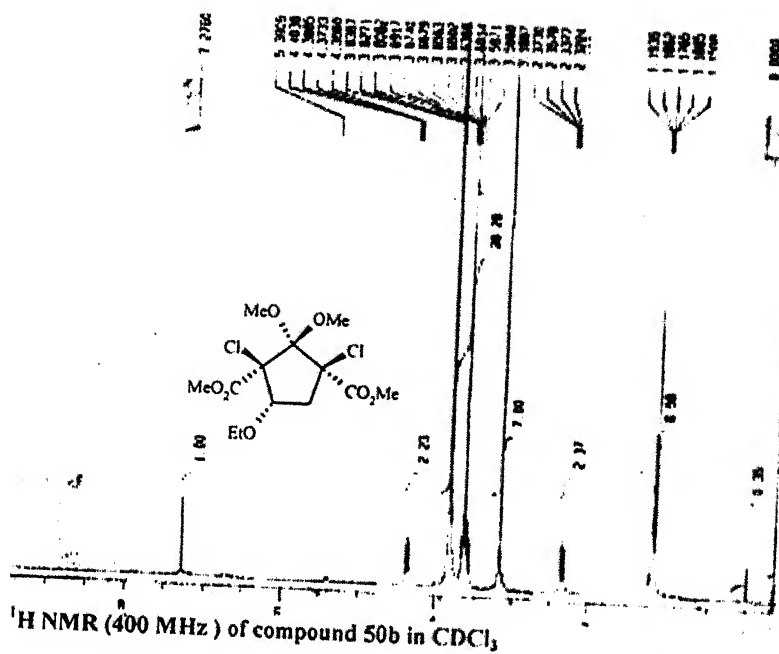
$J = 1.1, 3.5$  Hz), 3.03 (dd, 1H,  $J = 15.4, 5.1$ Hz), 2.32 (dd, 1H,  $J = 15.4, 9.2$  Hz);  $^{13}\text{C}$  NMR  $\delta$  200.7 (-C=O), 173.9 (O-C=O), 169.6 (O-C=O), 130.8, 120.2, 106.6, 88.7, 54.9,

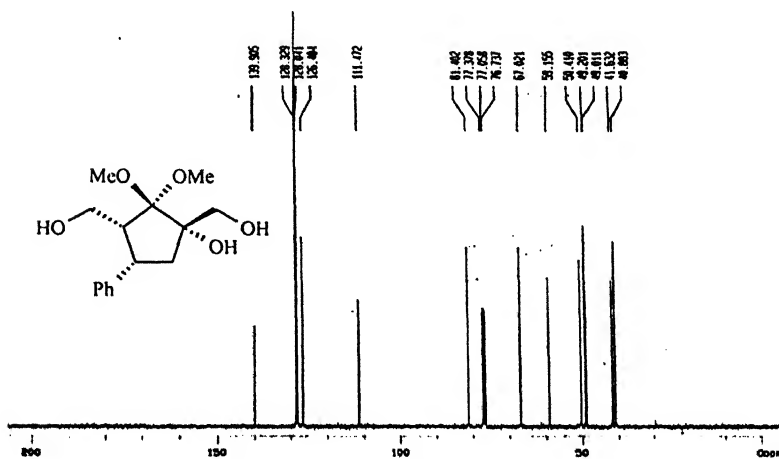
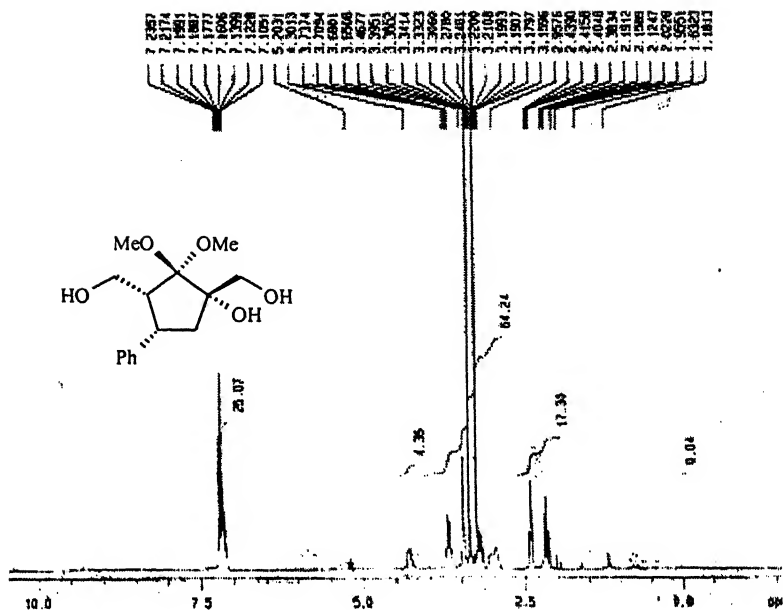
52.7, 51.5, 50.2, 49.4, 45.3, 43.1, 33.4; IR (KBr) 2950, 1760, 1700, 1610, 1360  $\text{cm}^{-1}$  ; Anal. Calcd. for  $\text{C}_{15}\text{H}_{18}\text{O}_7$ : C 58.06, H 5.85; Found C 58.10, H 5.88.

## Spectra

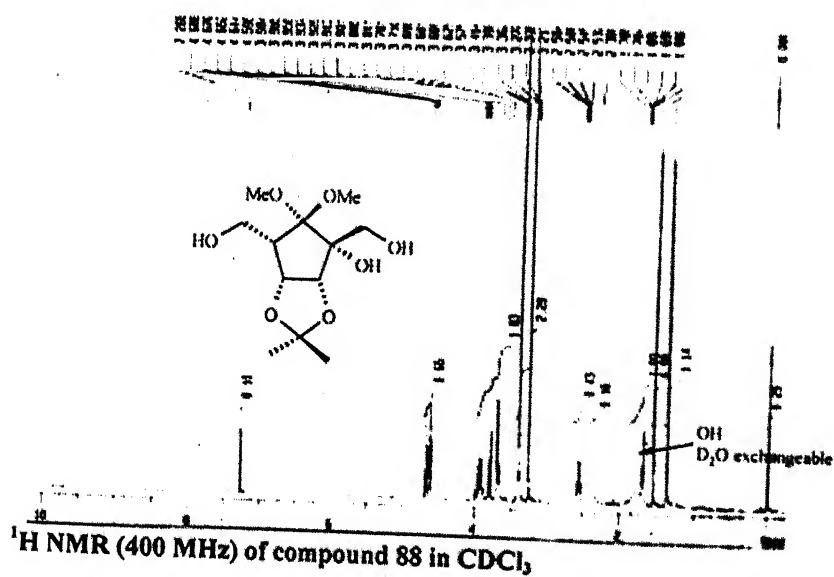
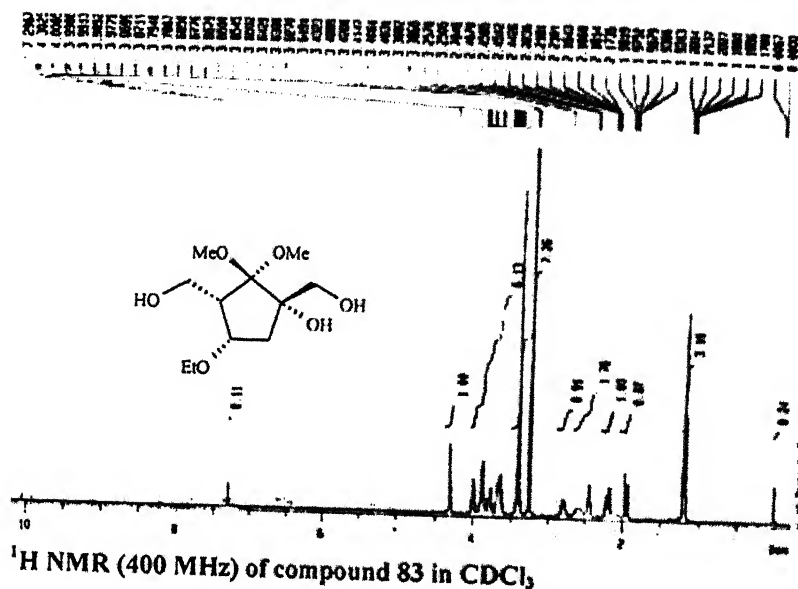


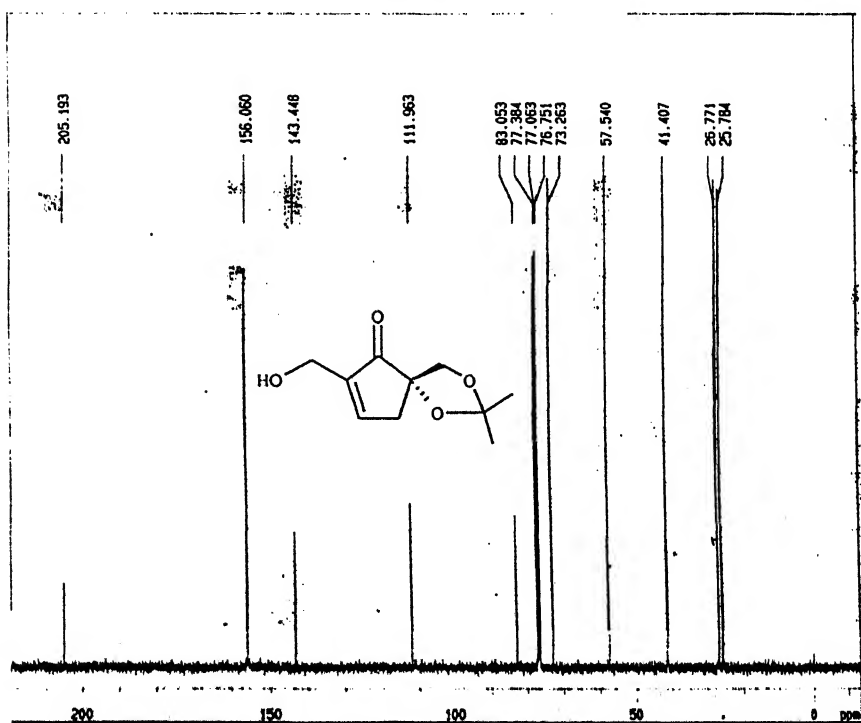
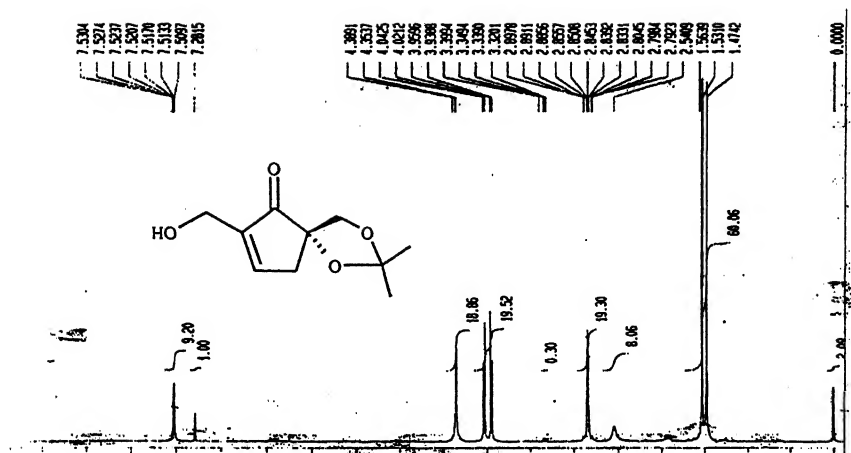
**<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) of compound 52b in CDCl<sub>3</sub>**





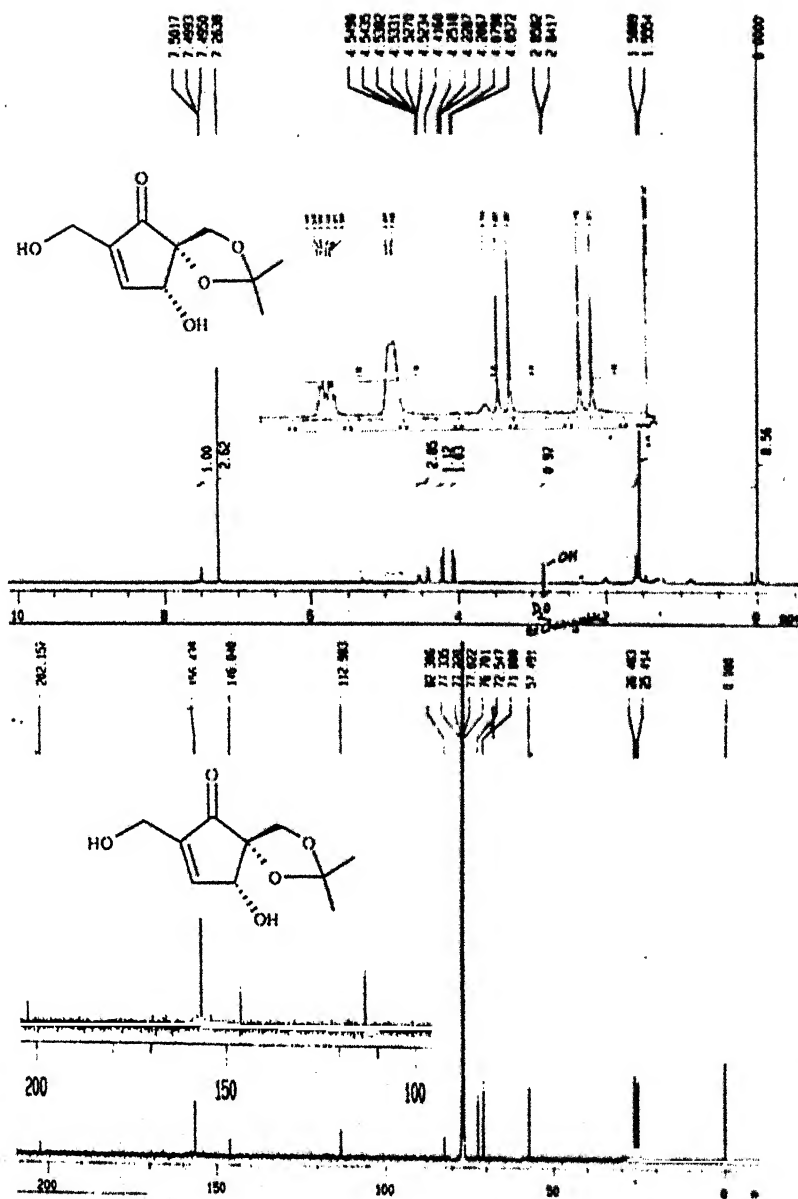
<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) of compound 81 in CDCl<sub>3</sub>



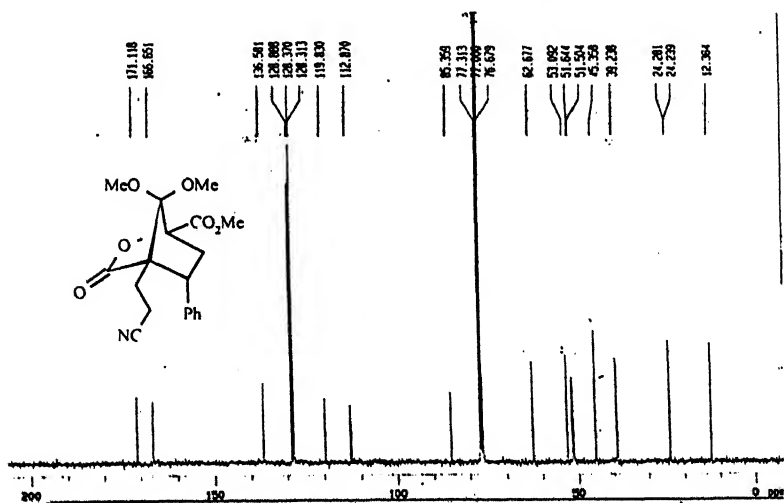
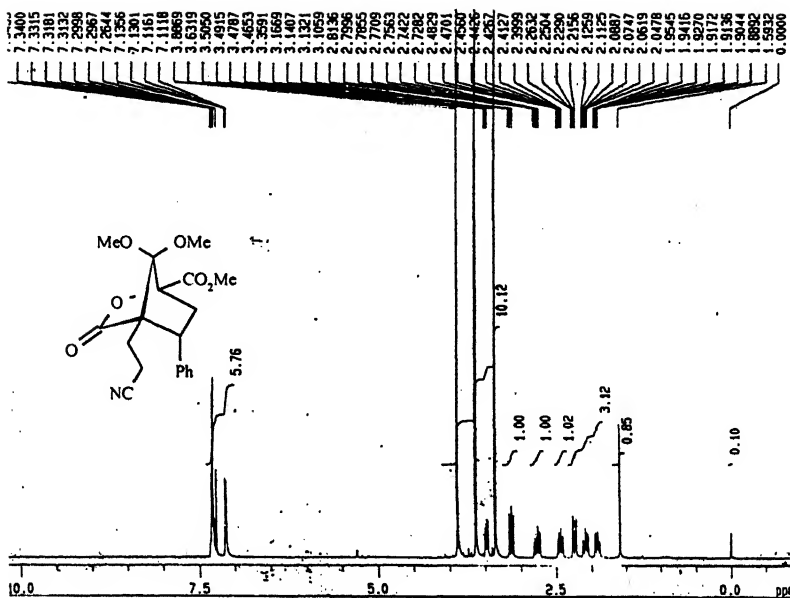


<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) of compound 48n CDCl<sub>3</sub>



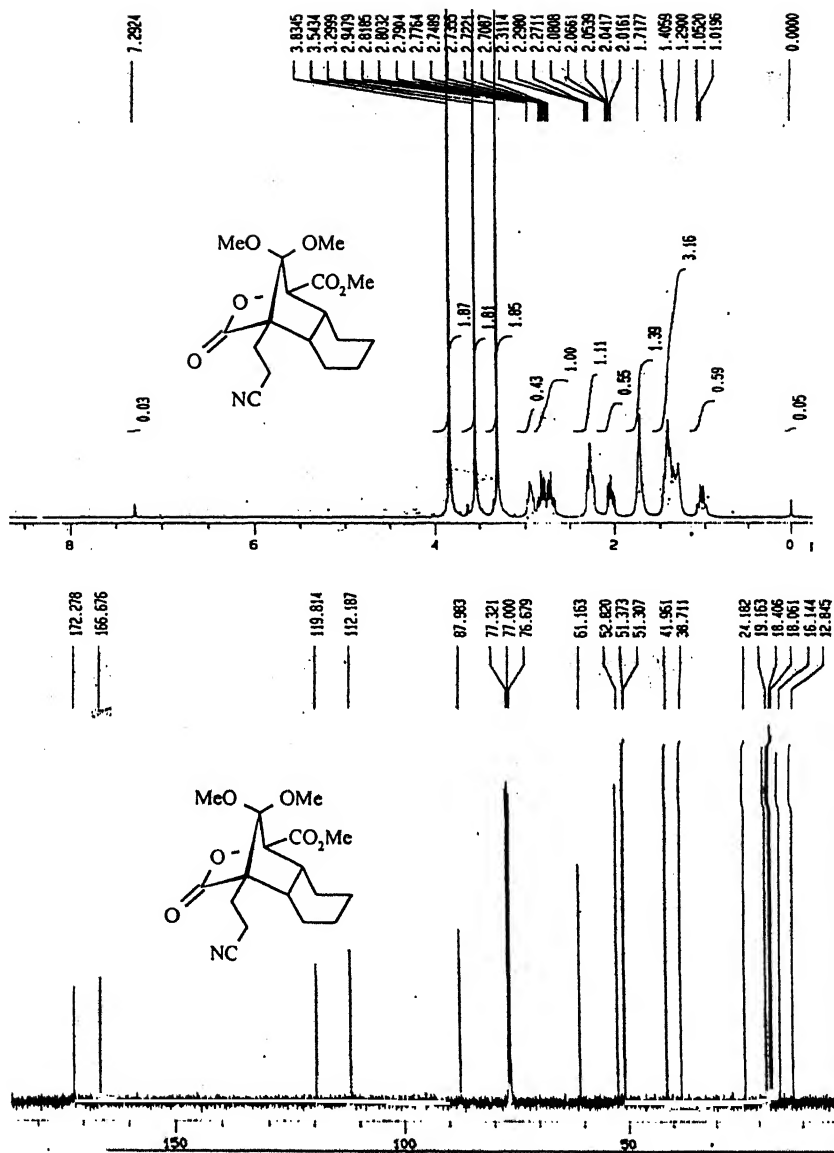


<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) of compound 49 in CDCl<sub>3</sub>

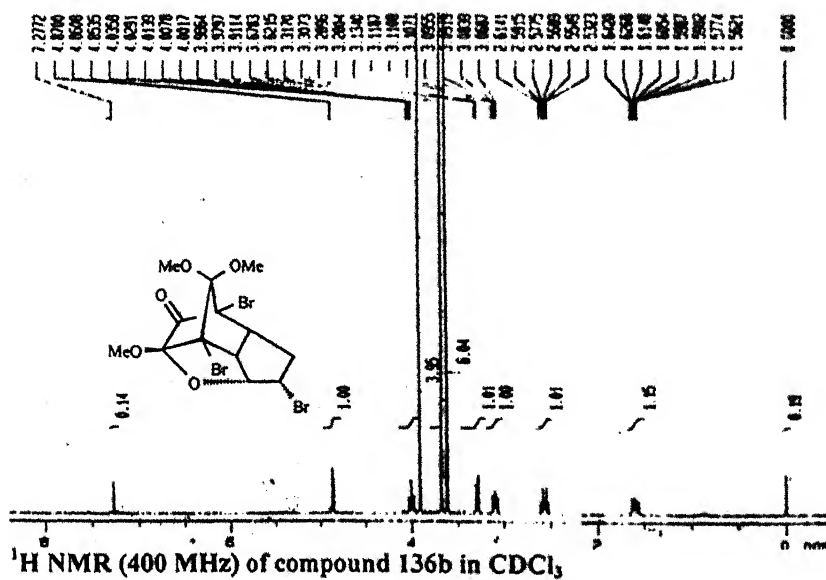
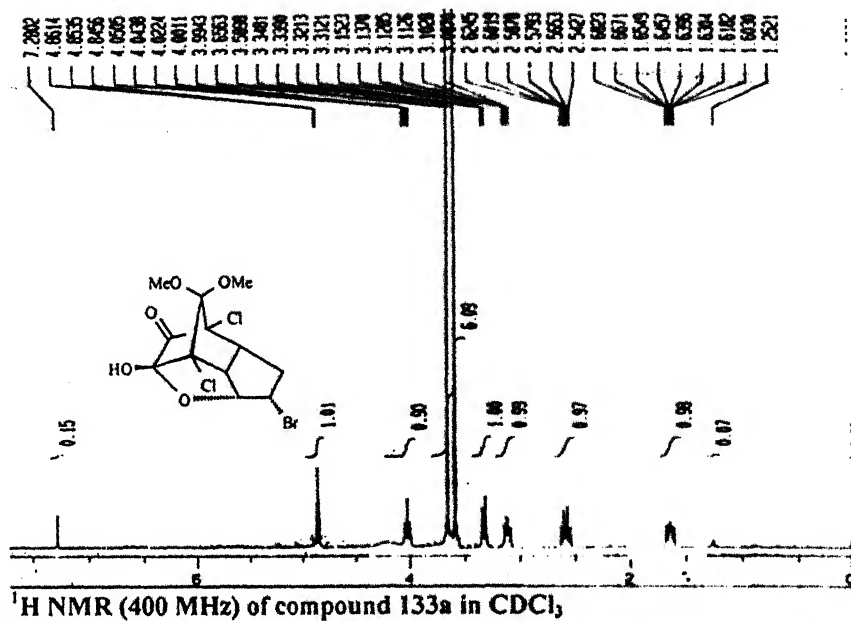


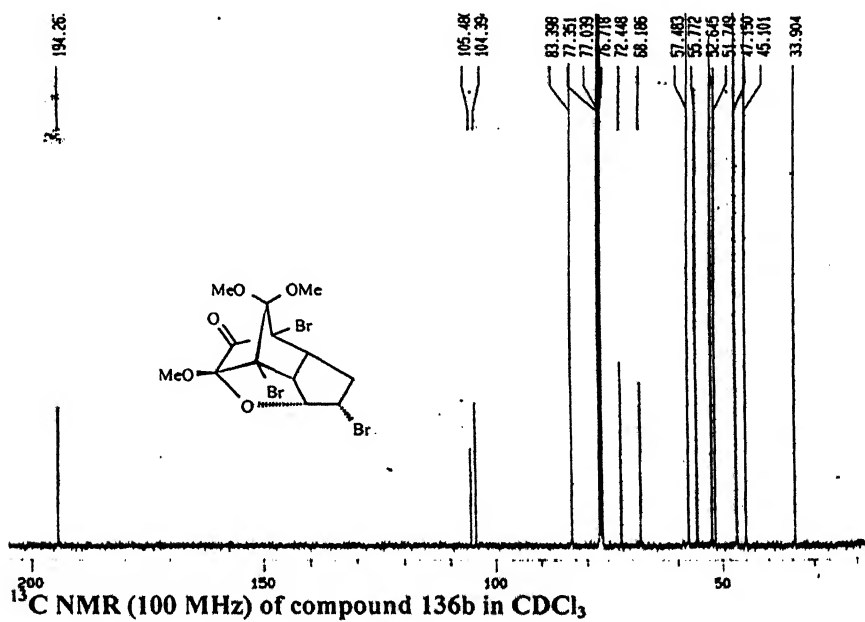
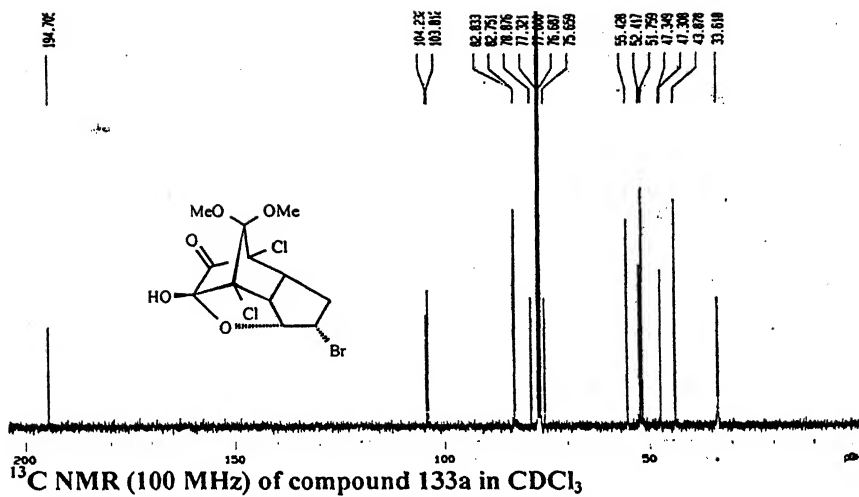
<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) of compound 112a in CDCl<sub>3</sub>

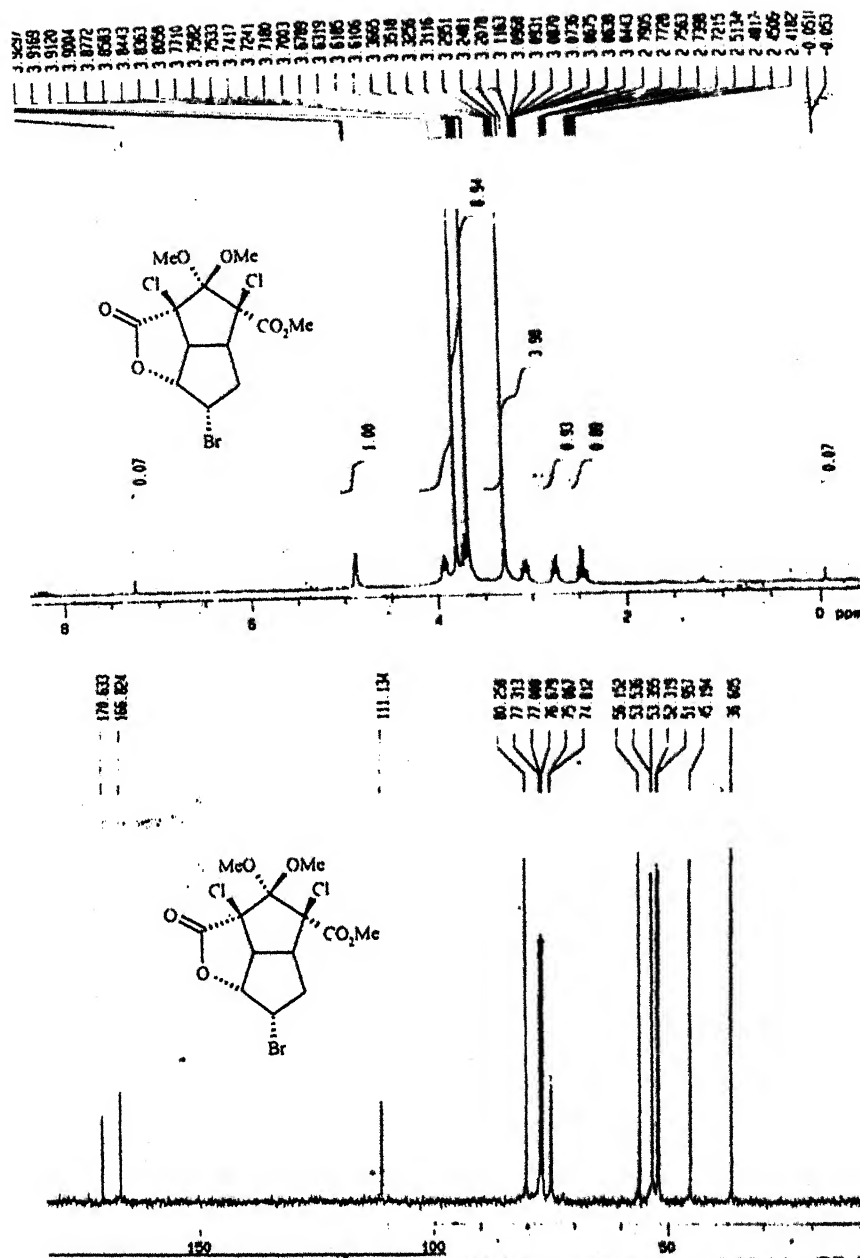


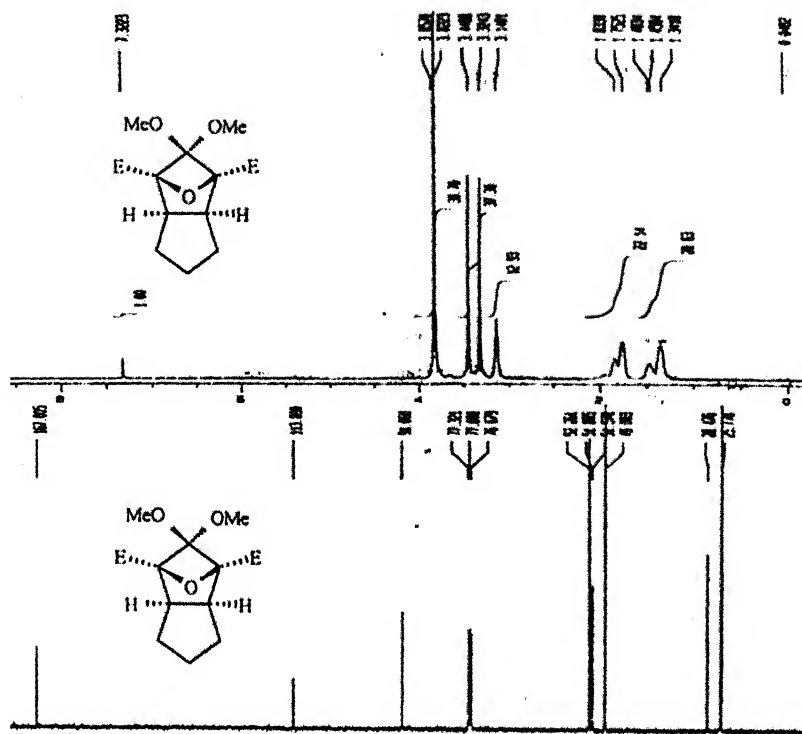


<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) of compound 112j in CDCl<sub>3</sub>

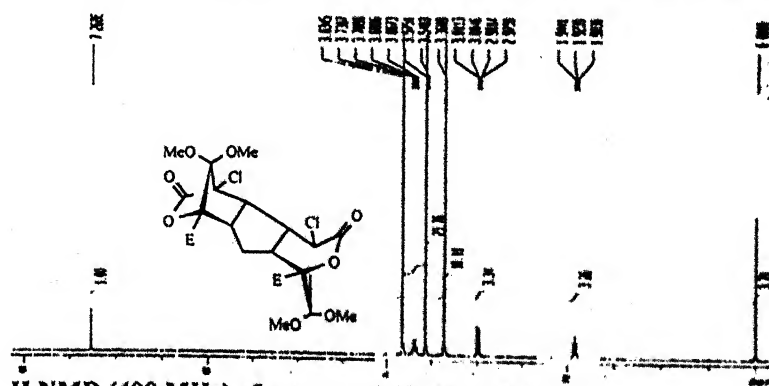






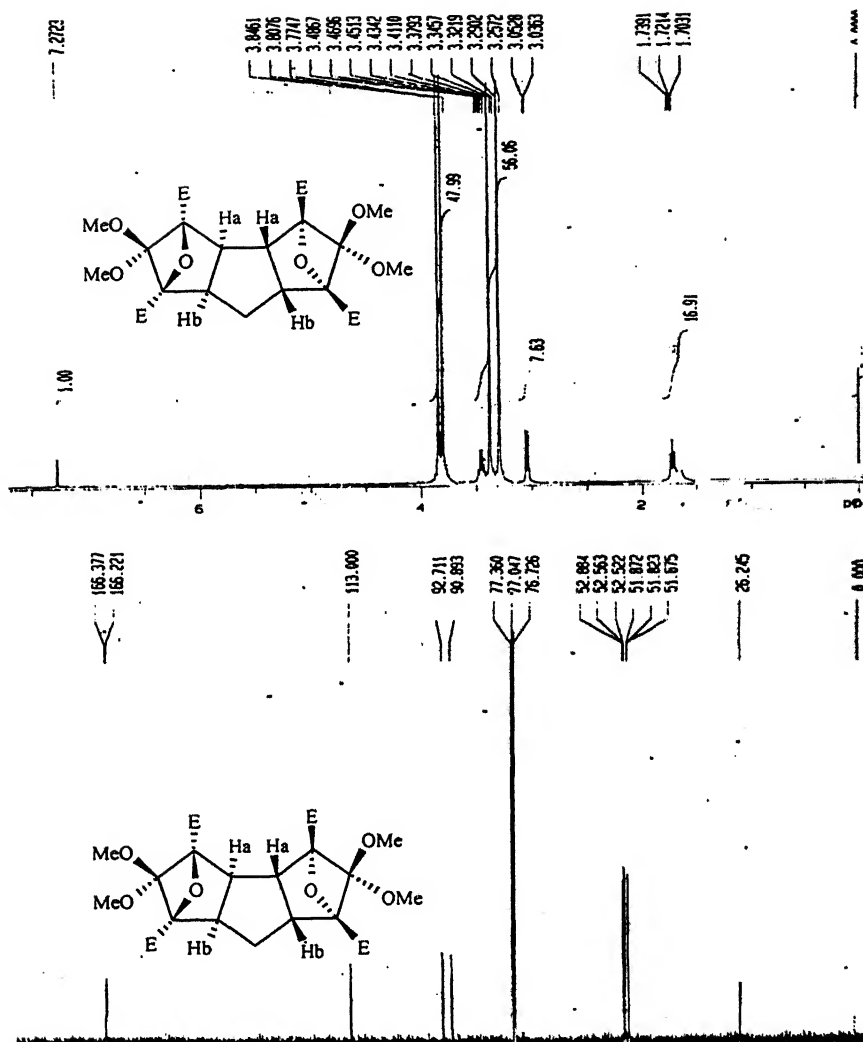


$^1\text{H}$  NMR (400 MHz) and  $^{13}\text{C}$  NMR (100 MHz) of compound 163i in  $\text{CDCl}_3$

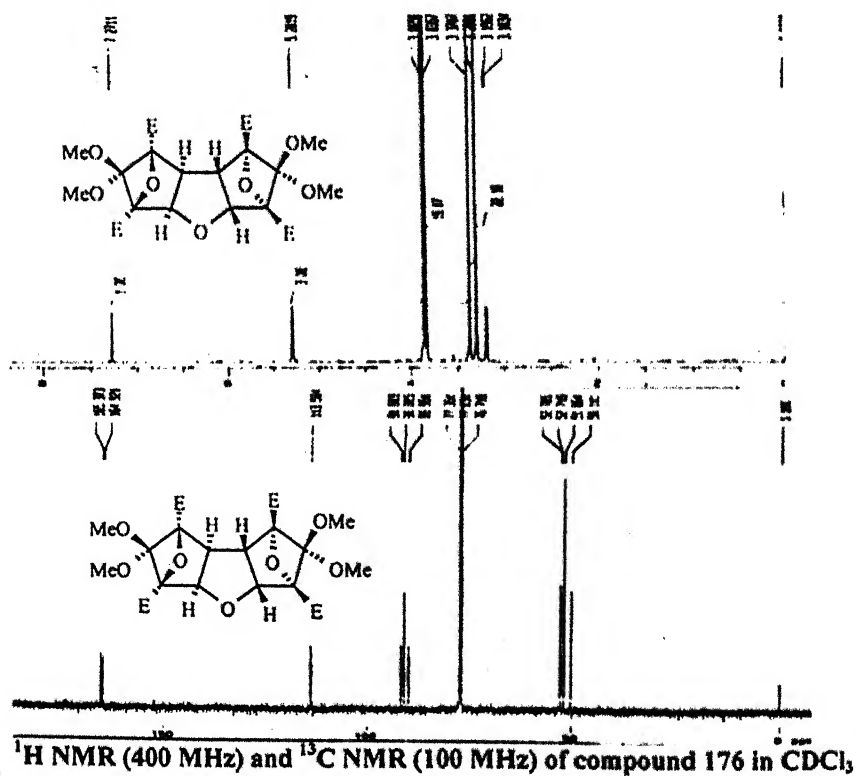
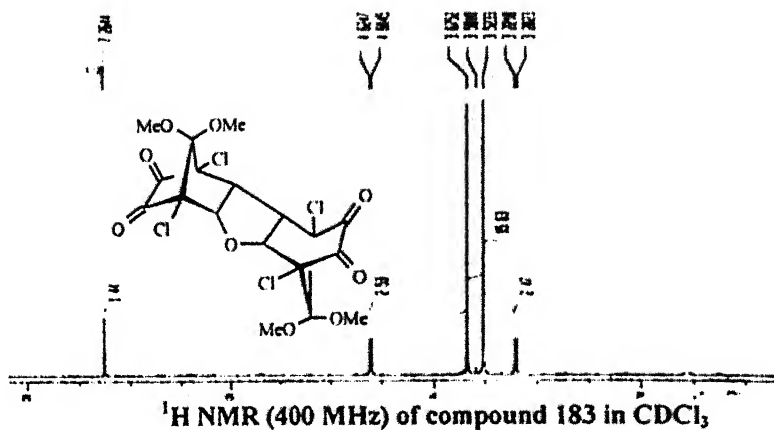


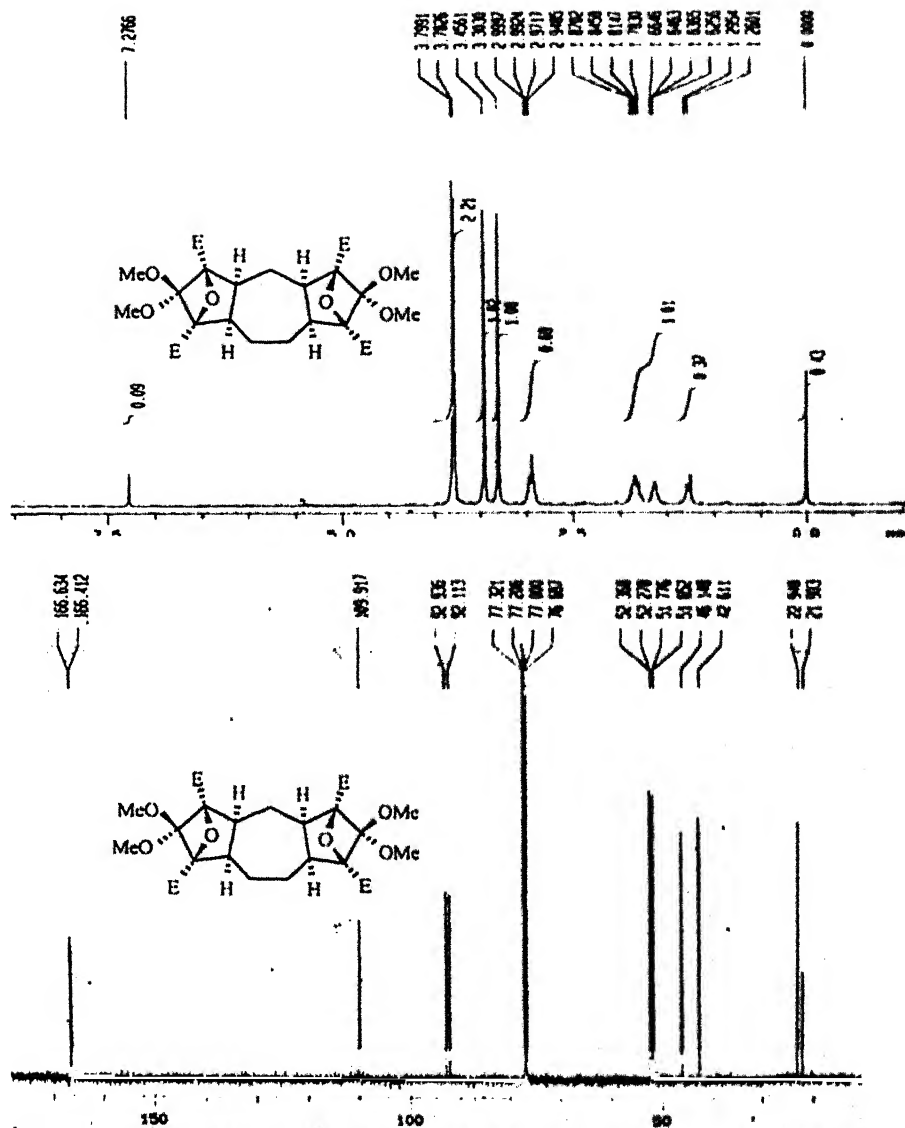
$^1\text{H}$  NMR (400 MHz) of compound 181 in  $\text{CDCl}_3$



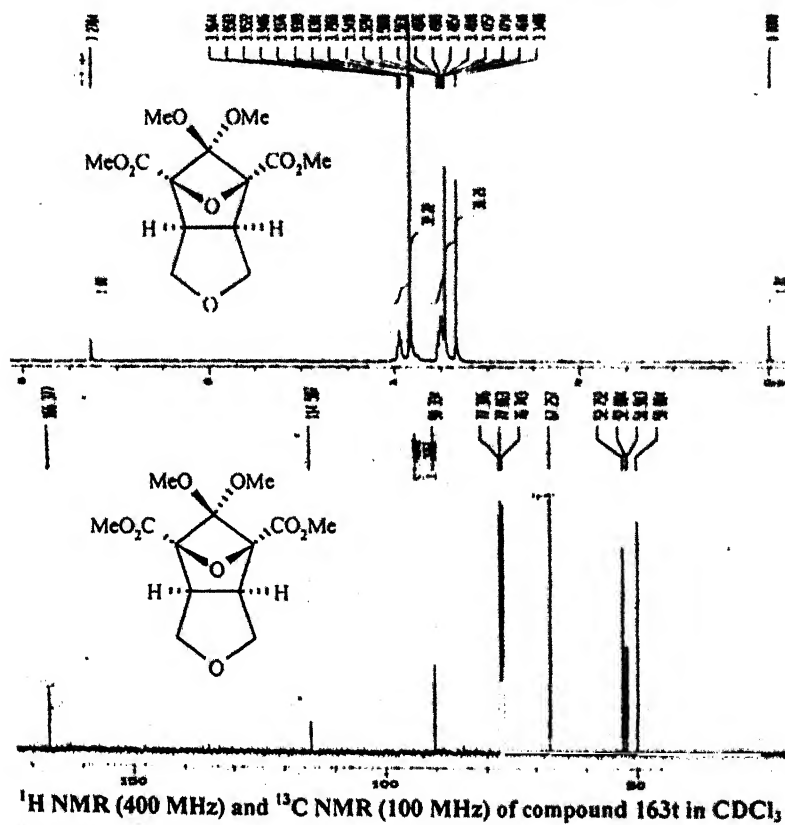
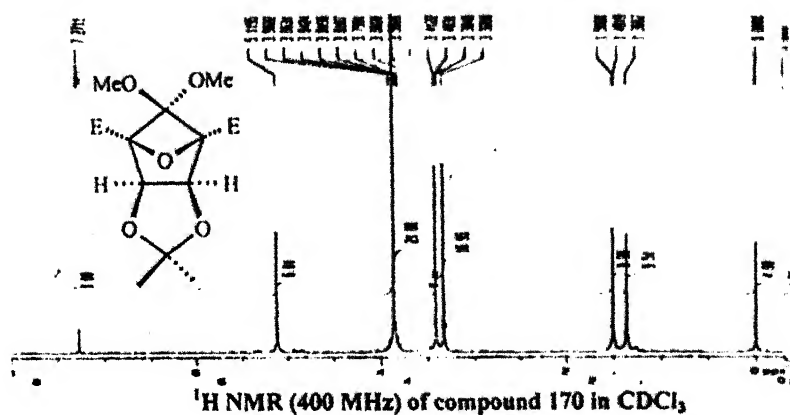


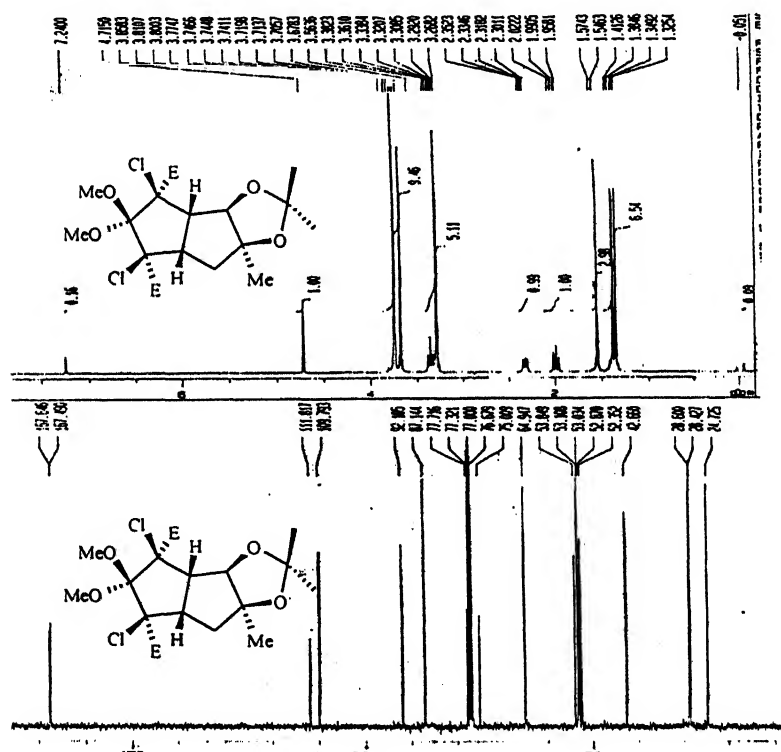
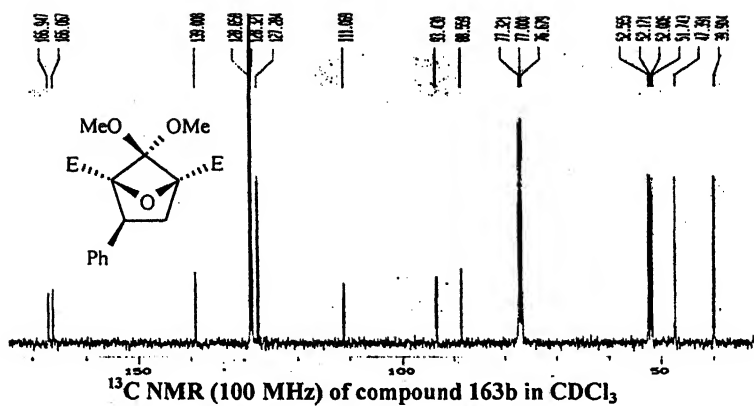
<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) of compound 175 in CDCl<sub>3</sub>

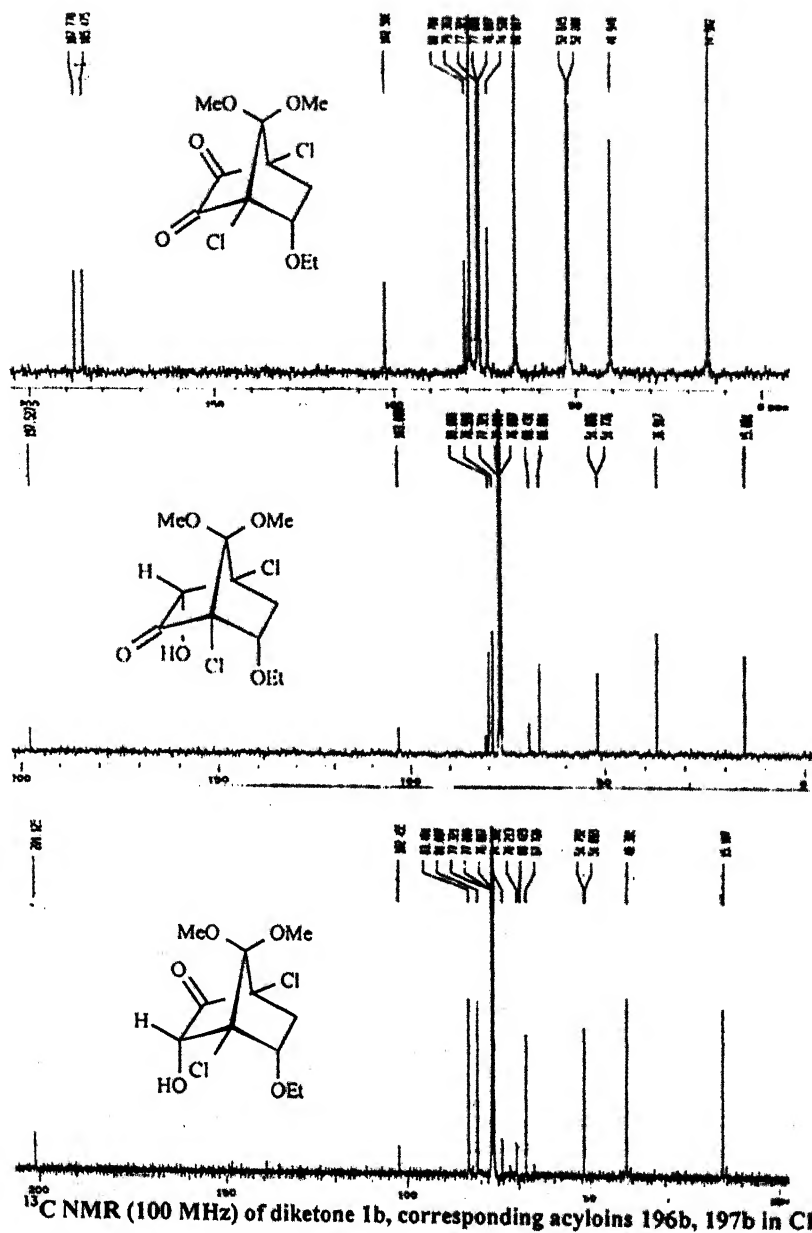




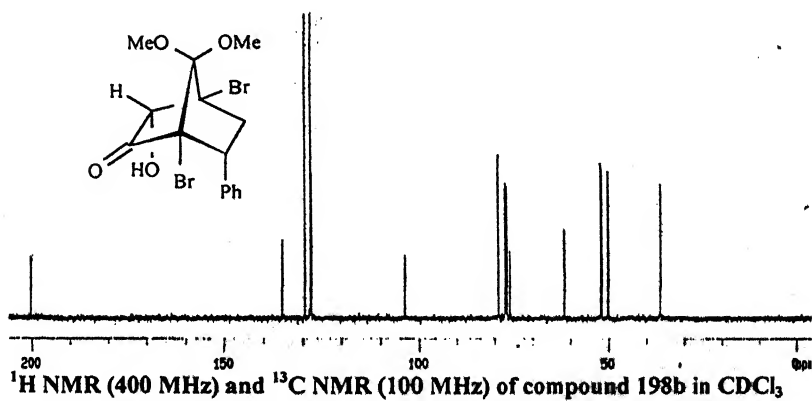
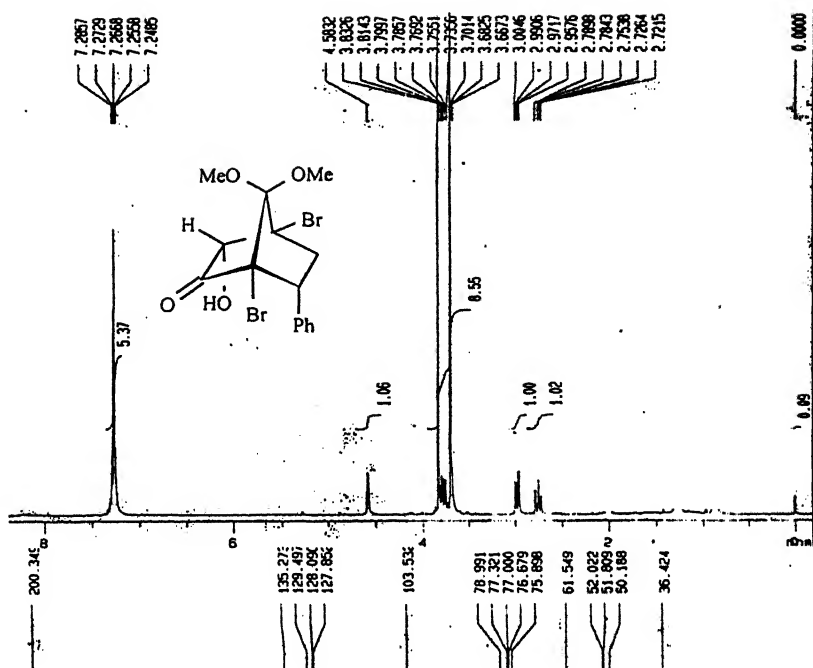
<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) of compound 174 in CDCl<sub>3</sub>.



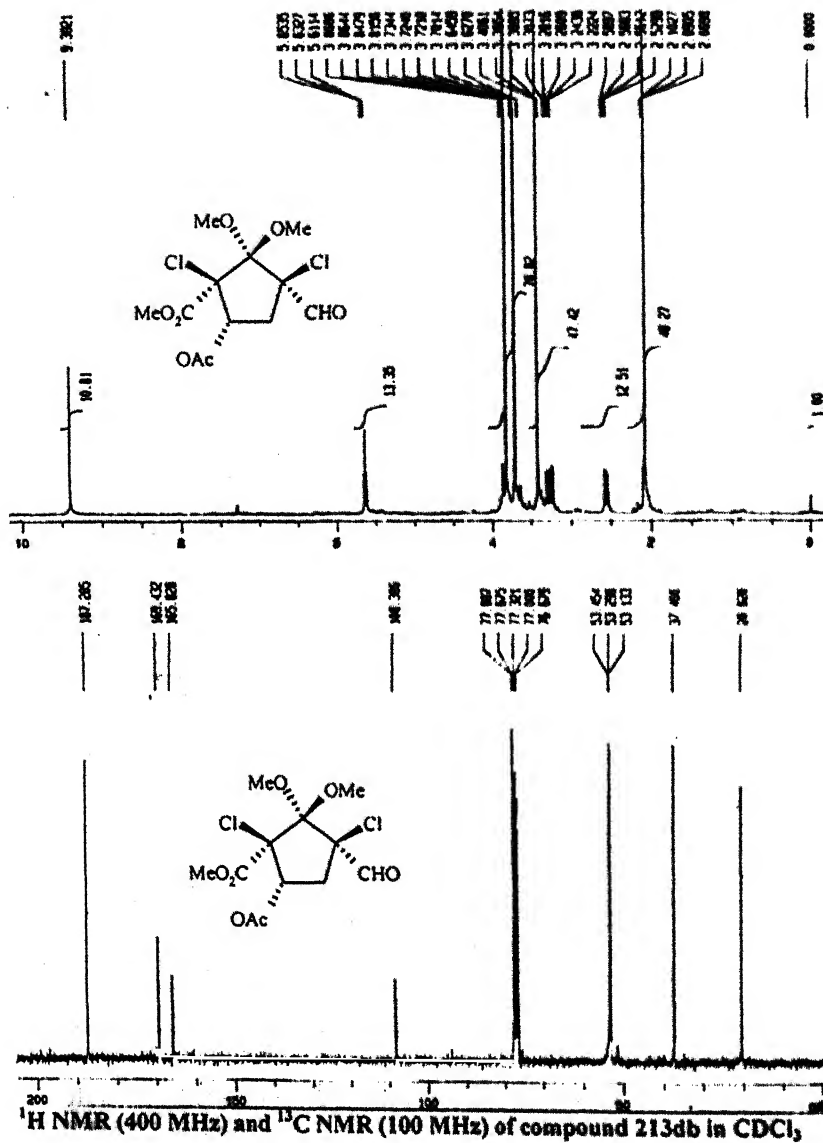




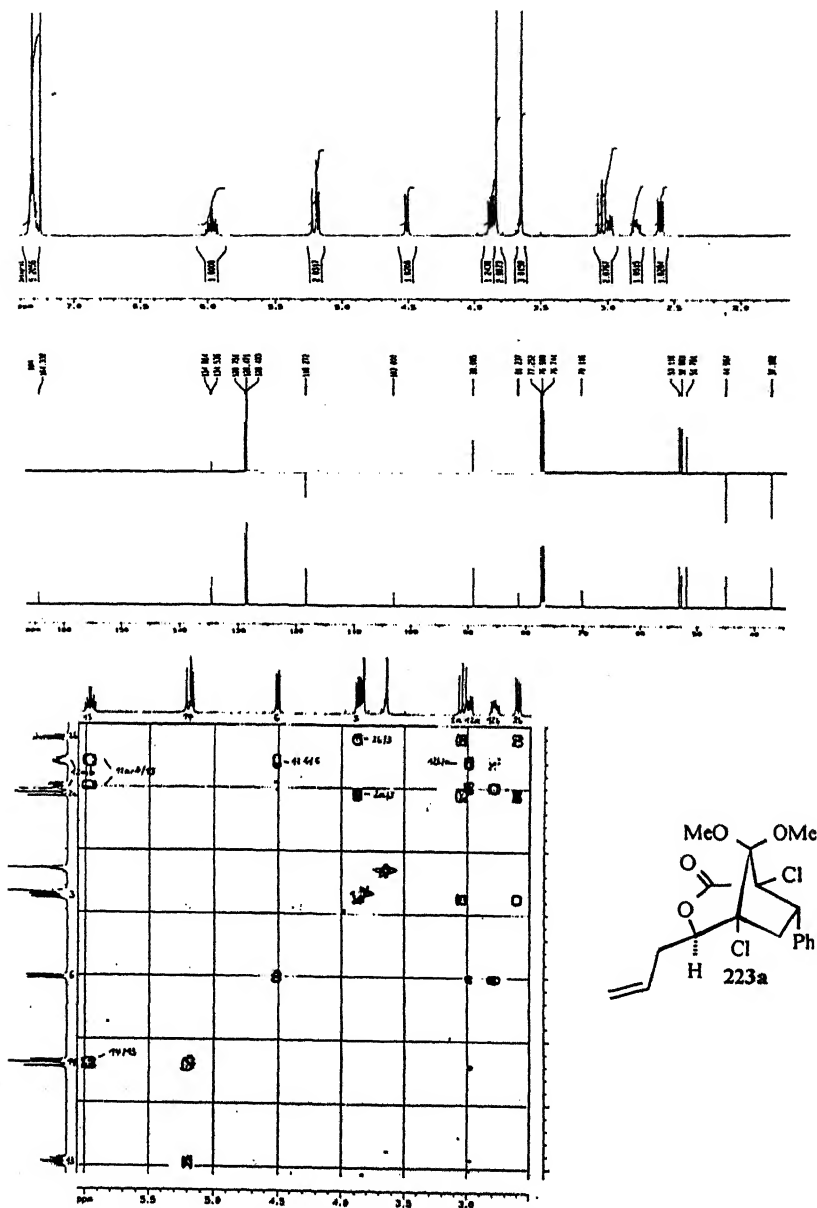
$^{13}\text{C}$  NMR (100 MHz) of diketone **1b**, corresponding acyloins **196b**, **197b** in  $\text{CDCl}_3$ .



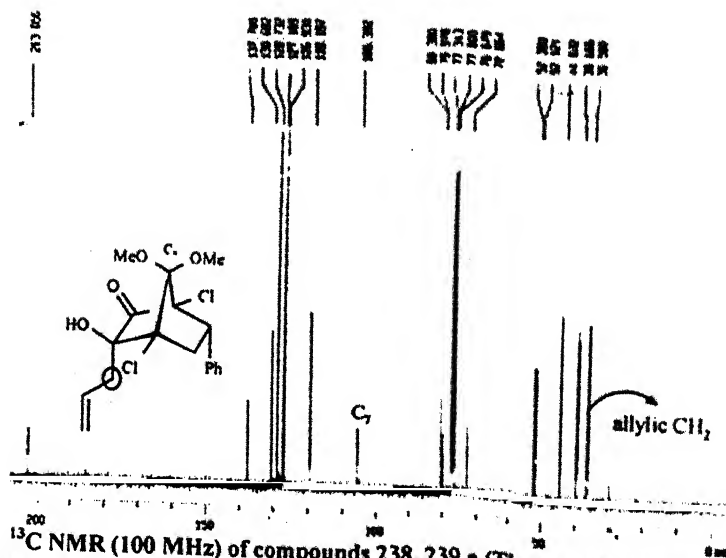
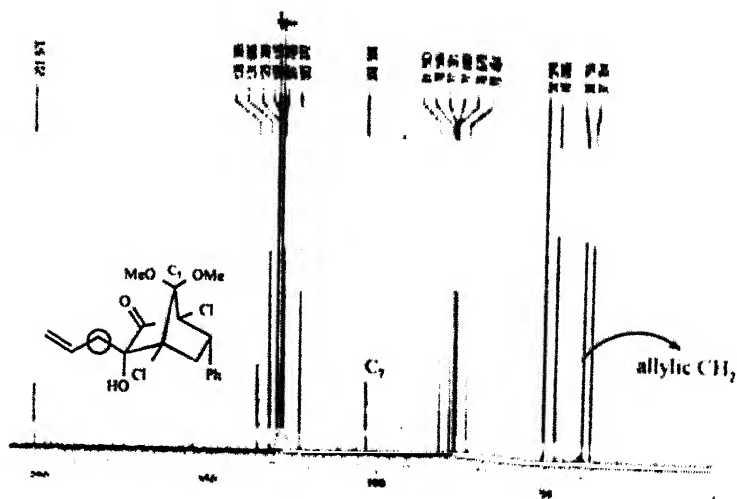
<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) of compound 198b in CDCl<sub>3</sub>



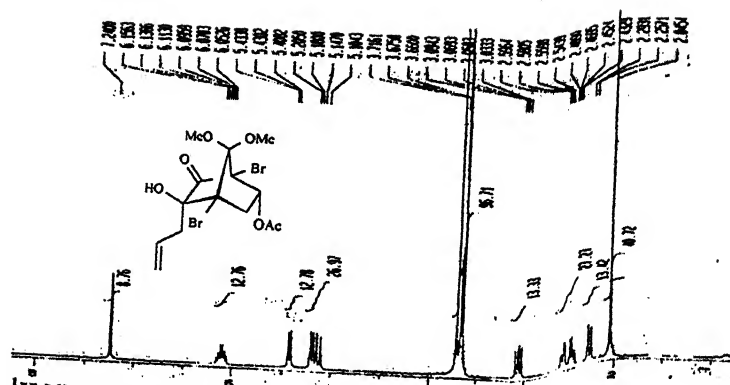




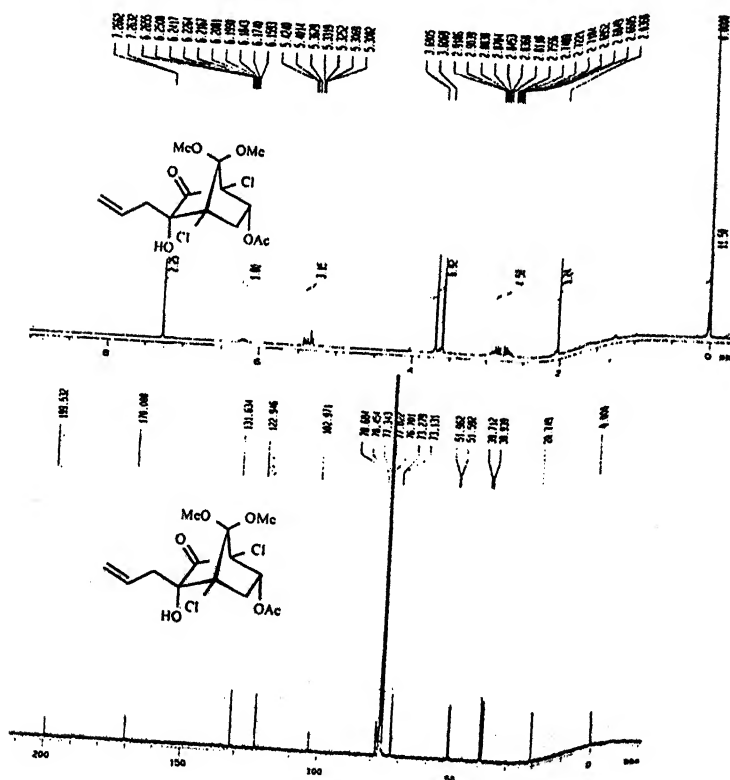
$^1\text{H}$  NMR (500 MHz),  $^{13}\text{C}$  NMR (100 MHz),  $^1\text{H}/^1\text{H}$  COSY spectrum of compound 223a in  $\text{CDCl}_3$



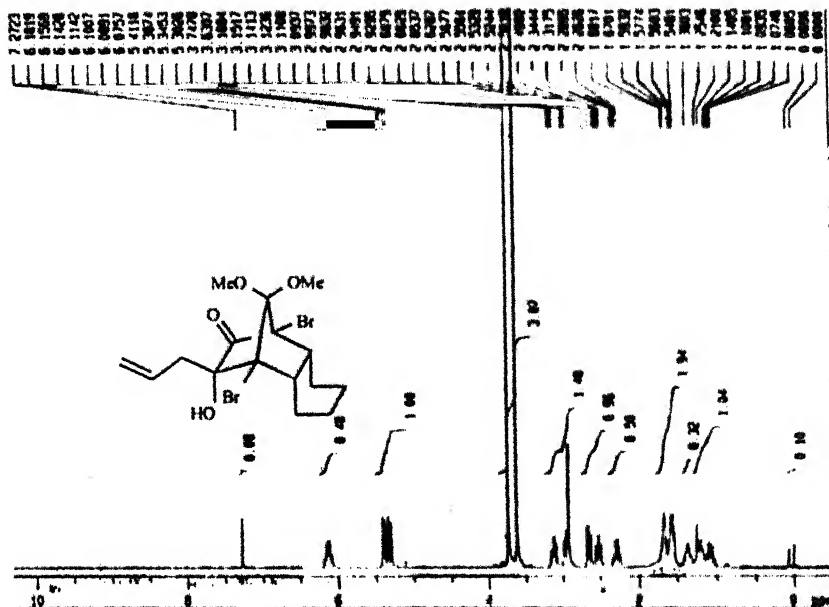
<sup>13</sup>C NMR (100 MHz) of compounds 238, 239 a (The two isomeric acyloins resulted from 1a) in CDCl<sub>3</sub>



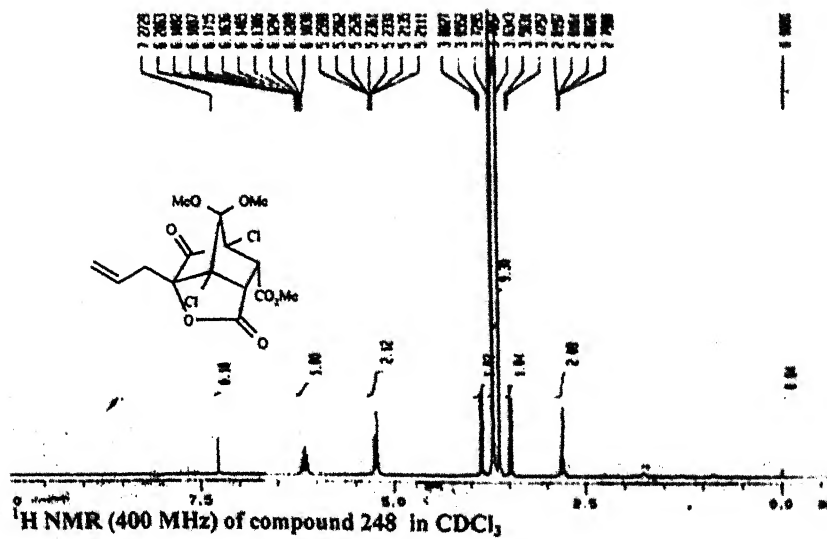
$^1\text{H}$  NMR (400 MHz) of compound 238d in  $\text{CDCl}_3$



<sup>1</sup>H NMR (400 MHz) and <sup>13</sup>C NMR (100 MHz) of compound 238d in CDCl<sub>3</sub>.



<sup>1</sup>H NMR (400 MHz) of compound 248 in CDCl<sub>3</sub>,



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## Appendix: A.1 Crystal data

**Table 1B.1. Crystal data and structure refinement for 105a<sup>§</sup>**

Parameters	Compound 105a
Empirical formula	C <sub>18</sub> H <sub>25</sub> NO <sub>5</sub>
Formula weight	335.39
Temperature	153 K
Wavelength	0.71073 Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	a = 12.314(2) Å   α = 90 ° b = 15.807(3) Å   β = 90 ° c = 17.894(3) Å   γ = 90 °
Volume, Z	3483.0(10) Å <sup>3</sup> , 8
Density (Calculated)	1.279 Mg/m <sup>3</sup>
Absorption coefficient	0.093 mm <sup>-1</sup>
F(000)	1440
Crystal size	0.8 x 0.45 x 0.2 mm
θ range for data collection	2.28 to 30.53 °
Index ranges	-17 ≤ h ≤ 17, -22 ≤ k ≤ 22, -24 ≤ l ≤ 25
Reflections collected	40740
Independent reflections	5310 [R(int) = 0.0319]
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	5310 / 0 / 220
Goodness-of-fit on F <sup>2</sup>	1.051
Final R indices [I > 2σ(I)]	R1 = 0.0390, wR2 = 0.1089
R indices (all data)	R1 = 0.0527, wR2 = 0.1219
Extinction coefficient	0.0010(4)
Largest diff. peak and hole	0.588 and -0.595 eÅ <sup>-3</sup>

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Table 2.1. Crystal data and structure refinement for 175<sup>a</sup>

Parameters	Compound 175
Empirical formula	C <sub>23</sub> H <sub>30</sub> O <sub>14</sub>
Formula weight	530.47
Temperature	293(2) K
Wavelength	0.70930 Å
Crystal system	Monoclinic
Space group	C1c1
Unit cell dimensions	a = 19.7410(15) Å   α = 90.000(7)° b = 9.5460(9) Å   β = 96.510(7)° c = 13.3000(11) Å   γ = 90.000(7)°
Volume, Z	2490.2(4) Å <sup>3</sup> , 4
Density (Calculated)	1.415 Mg/m <sup>3</sup>
Absorption coefficient	0.119 mm <sup>-1</sup>
F(000)	1120
θ range for data collection	.07 to 24.92°
Limiting indices	-22 ≤ h ≤ 23, 0 ≤ k ≤ 11, -15 ≤ l ≤ 0
Reflections collected	1652
Independent reflections	1652 [R(int) = 0.0000]
Absorption correction	None
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	1652 / 2 / 343
Goodness-of-fit on F <sup>2</sup>	1.010
Final R indices [I > 2σ(I)]	R1 = 0.0367, wR2 = 0.0678
R indices (all data)	R1 = 0.0726, wR2 = 0.0820
Extinction coefficient	0.0021(3)
Largest diff. peak and hole	0.174 and -0.174 eÅ <sup>-3</sup>

**Table 2.2. Crystal data and structure refinement for 181<sup>+</sup>**

Parameters	Compound 181
Empirical formula	$C_{21}H_{24}Cl_2O_{12}$
Formula weight	539.30
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Triclinic
Space group	P -1
Unit cell dimensions	$a = 8.062(5) \text{ Å}$ $\alpha = 104.681(5)^\circ$ $b = 10.868(5) \text{ Å}$ $\beta = 90.614^\circ$ $c = 13.771(5) \text{ Å}$ $\gamma = 102.133(5)^\circ$
Volume, Z	1138.5(10) Å <sup>3</sup> , 2
Density (Calculated)	1.573 Mg/m <sup>3</sup>
Absorption coefficient	0.352 mm <sup>-1</sup>
F(000)	560
$\theta$ range for data collection	1.53 to 24.97 °
Limiting indices	$0 \leq h \leq 9, -12 \leq k \leq 12, -16 \leq l \leq 16$
Reflections collected	4310
Independent reflections	3997 [R(int) = 0.0201]
Absorption correction	None
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	3997 / 0 / 323
Goodness-of-fit on F <sup>2</sup>	1.003
Final R indices [I > 2 $\sigma$ (I)]	R1 = 0.0491, wR2 = 0.1363
R indices (all data)	R1 = 0.0872, wR2 = 0.1530
Extinction coefficient	0.001(2)
Largest diff. peak and hole	0.367 and -0.360 eÅ <sup>-3</sup>

**Table 2.4. Crystal data and structure refinement for 176<sup>a</sup>**

Parameters	Compound 176
Empirical formula	C <sub>22</sub> H <sub>28</sub> O <sub>15</sub>
Formula weight	532.44
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	A = 8.142(5) Å   α = 95.894(5) ° B = 10.888 (5) Å   β = 99.268(5) ° C = 14.672(5) Å   γ = 102.143(5) °
Volume, Z	1242.3(10) Å <sup>3</sup> , 2
Density (Calculated)	1.423 Mg/m <sup>3</sup>
Absorption coefficient	0.122 mm <sup>-1</sup>
F(000)	560
θ range for data collection	1.42 to 24.97 °
Limiting indices	-9 ≤ h ≤ 9, -12 ≤ k ≤ 0, -17 ≤ l ≤ 17
Reflections collected	4629
Independent reflections	4374 [R(int) = 0.0143]
Absorption correction	None
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	4374 / 0 / 343
Goodness-of-fit on F <sup>2</sup>	1.077
Final R indices [I > 2σ(I)]	R1 = 0.0435, wR2 = 0.1134
R indices (all data)	R1 = 0.0859, wR2 = 0.1209
Extinction coefficient	0.0063(16)
Largest diff. peak and hole	0.225 and -0.184 eÅ <sup>-3</sup>

Table 3B.1. Crystal data and structure refinement for 238e<sup>a</sup>

Parameters	Compound 238e
Empirical formula	C <sub>15</sub> H <sub>24</sub> Cl <sub>7</sub> O <sub>4</sub> Si
Formula weight	367.33
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	P212121
Unit cell dimensions	a = 11.686 Å α = 90° b = 12.807 Å β = 90.136° c = 12.280 (5) Å γ = 90°
Volume, Z	1837.9(13) Å <sup>3</sup> , 4
Density (Calculated)	1.328 Mg/m <sup>3</sup>
Absorption coefficient	0.432 mm <sup>-1</sup>
F(000)	776
θ range for data collection	2.30 to 25.25°
Limiting indices	-14 ≤ h ≤ 14, -14 ≤ k ≤ 0, -13 ≤ l ≤ 0
Reflections collected	3166
Independent reflections	2877 [R(int) = 0.0811]
Absorption correction	None
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	2877 / 0 / 206
Goodness-of-fit on F <sup>2</sup>	0.944
Final R indices [I > 2σ(I)]	R1 = 0.0574, wR2 = 0.1324
R indices (all data)	R1 = 0.1410, wR2 = 0.1582
Extinction coefficient	0.028(3)
Largest diff. peak and hole	0.239 and -0.293 e Å <sup>-3</sup>

**Table 3B.2. Crystal data and structure refinement for OAC\***

Parameters	Compound 239d
Empirical formula	C <sub>14</sub> H <sub>18</sub> C <sub>7</sub> O <sub>6</sub>
Formula weight	353.185
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Monoclinic
Space group	P121\1
Unit cell dimensions	a = 14.233(5) Å $\alpha$ = 90.000(5) ° b = 10.909(5) Å $\beta$ = 108.626(5) ° c = 21.821(5) Å $\gamma$ = 90.000(5) °
Volume, Z	3211(2) Å <sup>3</sup> , 4
Density (Calculated)	1.461 Mg/m <sup>3</sup>
Absorption coefficient	0.429 mm <sup>-1</sup>
F(000)	1472
$\theta$ range for data collection	1.97 to 24.98 °
Limiting indices	$16 \leq h \leq 0, 0 \leq k \leq 12, -24 \leq l \leq 25$
Reflections collected	5875
Independent reflections	5623 [R(int) = 0.0975]
Absorption correction	None
Refinement method	Full-matrix least-squares on F <sup>2</sup>
Data / restraints / parameters	5623 / 0 / 406
Goodness-of-fit on F <sup>2</sup>	0.932
Final R indices [ $I > 2\sigma(I)$ ]	R1 = 0.0556, wR2 = 0.1466
R indices (all data)	R1 = 0.1679, wR2 = 0.1915
Extinction coefficient	0.0000(4)
Largest diff. peak and hole	0.366 and -0.405 eÅ <sup>-3</sup>

**Table 3B.3. Crystal data and structure refinement for 244\***

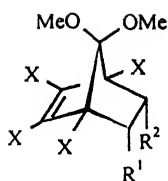
Parameters	Compound 244
Empirical formula	$C_{19}H_{22}Cl_2O_4$
Formula weight	385.27
Temperature	293(2) K
Wavelength	0.71069 Å
Crystal system	Orthorhombic
Space group	Pbca
Unit cell dimensions	$a = 10.477 \text{ Å}$ $\alpha = 90^\circ$ $b = 13.687 \text{ Å}$ $\beta = 90^\circ$ $c = 12.280 \text{ Å}$ $\gamma = 90^\circ$
Volume, Z	$3678(2) \text{ Å}^3$ , 8
Density (Calculated)	$1.392 \text{ Mg/m}^3$
Absorption coefficient	$0.374 \text{ mm}^{-1}$
F(000)	1616
$\theta$ range for data collection	$1.59$ to $22.47^\circ$
Limiting indices	$0 \leq h \leq 11$ , $0 \leq k \leq 14$ , $0 \leq l \leq 27$
Reflections collected	2402
Independent reflections	2402 [ $R(\text{int}) = 0.0000$ ]
Absorption correction	None
Refinement method	Full-matrix least-squares on $F^2$
Data / restraints / parameters	2402 / 0 / 231
Goodness-of-fit on $F^2$	1.056
Final R indices [ $I > 2\sigma(I)$ ]	$R1 = 0.0344$ , $wR2 = 0.0892$
R indices (all data)	$R1 = 0.0643$ , $wR2 = 0.1016$
Extinction coefficient	$0.0027(4)$
Largest diff. peak and hole	$0.229$ and $-0.298 \text{ e Å}^{-3}$

\*The solvent of crystallization and melting point of the crystal is given in the experimental section. The structure was solved by WinGX - Version 1.64.03a, An Integrated System of Windows Programs for the Solution, Refinement and Analysis of Single Crystal X-Ray Diffraction Data by Louis J. Farrugia, Dept. of Chemistry, University of Glasgow (1997-2002). L. J. Farrugia, J. Appl.

Cryst. (1999) 32, 837-838. The structure was solved initially with SIR97 and then refined with SHELX-97, which are incorporated in WinGX. The structure was refined by full-matrix least-squares methods on  $F^2$ . The hydrogen atom positions were initially determined by geometry and refined by a riding model. Non-hydrogen atoms were refined with anisotropic displacement parameters.



# List of New Compounds

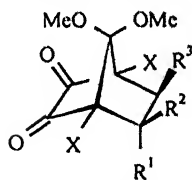


X=Cl, R<sup>1</sup>, R<sup>2</sup>

- 3e TMS, H  
 3r (CH<sub>2</sub>)<sub>2</sub>Br, H  
 3s (CH<sub>2</sub>)<sub>3</sub>Br, H  
 3i -(CH<sub>2</sub>)<sub>3</sub>-  
 3p -OC(CH<sub>3</sub>)<sub>2</sub>O-  
 166 -(CH<sub>2</sub>-CH  
 (Me)-CH<sub>2</sub>)  
 190 CHO, CH<sub>2</sub>COMe

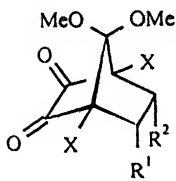
X=Br, R<sup>1</sup>, R<sup>2</sup>

- 4b OEt, H  
 4e TMS, H  
 4g CH<sub>2</sub>Br, H  
 4i -(CH<sub>2</sub>)<sub>3</sub>-  
 4k -(CH<sub>2</sub>)<sub>4</sub>-  
 4n -OC(O)O-  
 4o OH, OH  
 4p -OC(CH<sub>3</sub>)<sub>2</sub>O-



X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>

- 57 Cl, E, H, Me  
 59 Cl, Ph, Me, H  
 60 Br, Ph, Me, H  
 68 Cl, E, Me, H  
 69 Br, E, Me, H  
 E=CO<sub>2</sub>Me

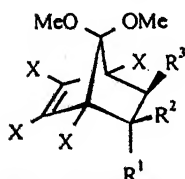


X=Cl, R<sup>1</sup>, R<sup>2</sup>

- 1b OEt, H  
 1e TMS, H  
 1g CH<sub>2</sub>Br, H  
 1h CH<sub>2</sub>Cl, H  
 1r (CH<sub>2</sub>)<sub>2</sub>Br, H  
 1s (CH<sub>2</sub>)<sub>3</sub>Br, H  
 1i -(CH<sub>2</sub>)<sub>3</sub>-  
 1k -(CH<sub>2</sub>)<sub>4</sub>-  
 1p -OC(CH<sub>3</sub>)<sub>2</sub>O-  
 167 -(CH<sub>2</sub>-CH  
 (Me)-CH<sub>2</sub>)

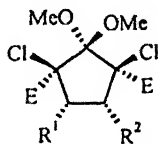
X=Br, R<sup>1</sup>, R<sup>2</sup>

- 2b OEt, H  
 2e TMS, H  
 2g CH<sub>2</sub>Br, H  
 2h CH<sub>2</sub>Cl, H  
 2i -(CH<sub>2</sub>)<sub>3</sub>-  
 2k -(CH<sub>2</sub>)<sub>4</sub>-  
 2p -OC(CH<sub>3</sub>)<sub>2</sub>O-

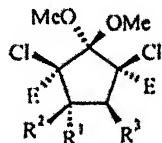
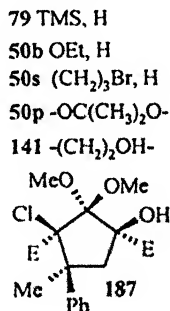


X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>

- 59 Cl, Ph, Me, H  
 60 Br, Ph, Me, H  
 67 Br, E, Me, H

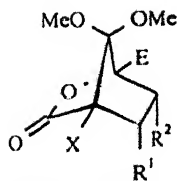
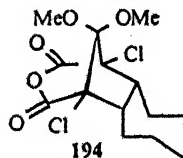
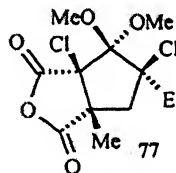


R<sup>1</sup>, R<sup>2</sup>



R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>

- 58 E, H, Me  
 64 Ph, Me, H  
 72 E, Me, H

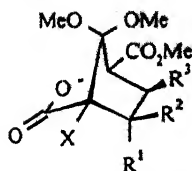


X=Cl, R<sup>1</sup>, R<sup>2</sup>

- 51a Ph, H  
 51b OEt, H  
 51p -OC(CH<sub>3</sub>)<sub>2</sub>O-  
 51i -(CH<sub>2</sub>)<sub>3</sub>-  
 51k -(CH<sub>2</sub>)<sub>4</sub>-  
 168 -(CH<sub>2</sub>-CH  
 (Me)-CH<sub>2</sub>)

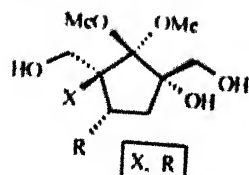
X=Br, R<sup>1</sup>, R<sup>2</sup>

- 52a Ph, H  
 52b OEt, H  
 52p -OC(CH<sub>3</sub>)<sub>2</sub>O-  
 52i -(CH<sub>2</sub>)<sub>3</sub>-  
 52k -(CH<sub>2</sub>)<sub>4</sub>-



X, R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>

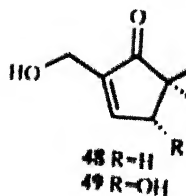
- 65 Cl, Ph, Me, H  
 63 Br, Ph, Me, H  
 76 Cl, E, Me, H  
 73 Br, E, Me, H  
 114 H, Ph, Me, H  
 113 (CH<sub>2</sub>)<sub>2</sub>CN, Ph,  
 Me, H



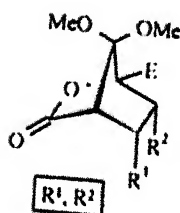
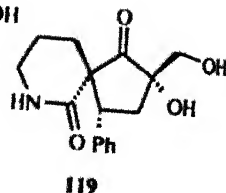
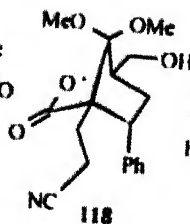
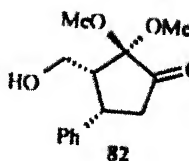
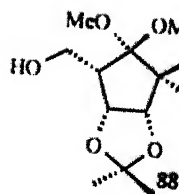
81 H, Ph

83 H, OEt

84 Cl, OEt

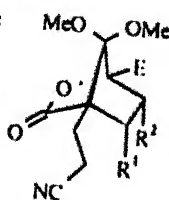


89



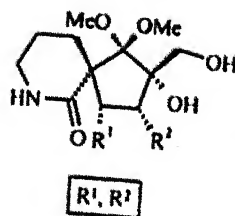
55a Ph, H

55b OEt, H

55p -OC(Me)<sub>2</sub>O-116 -(CH<sub>2</sub>)<sub>3</sub>

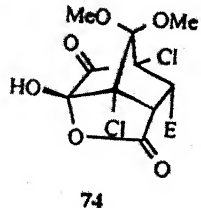
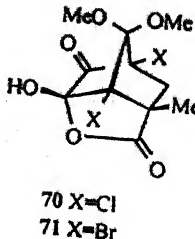
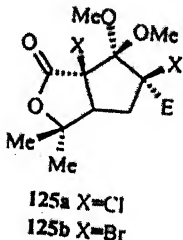
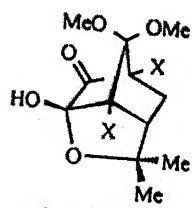
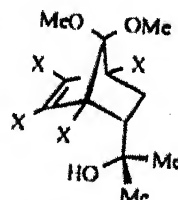
112a Ph, H

112b OEt, H

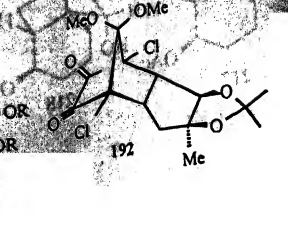
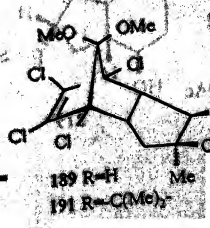
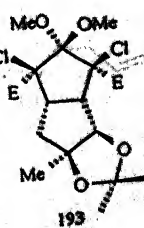
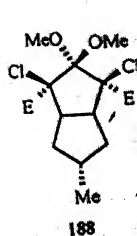
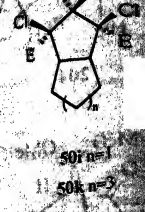
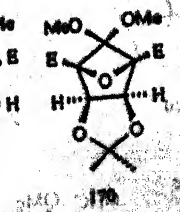
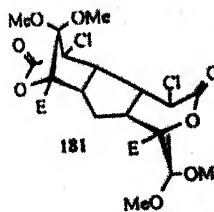
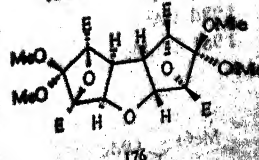
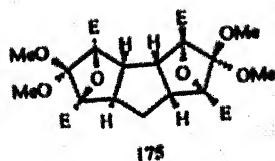
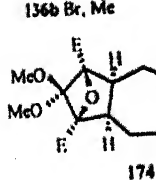
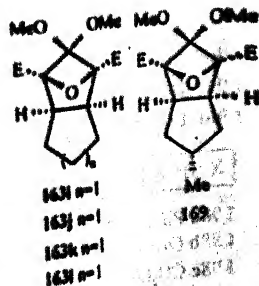
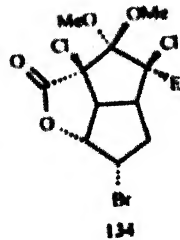
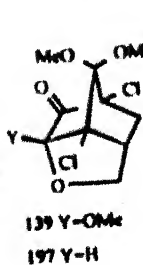
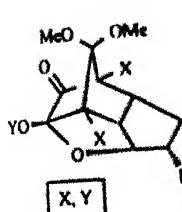
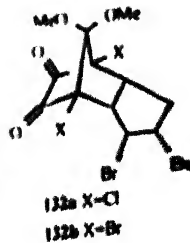
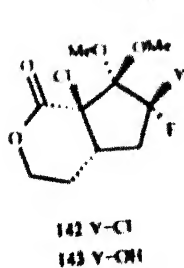
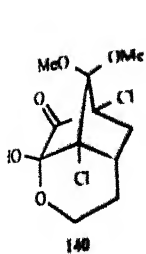
112j -(CH<sub>2</sub>)<sub>3</sub>-

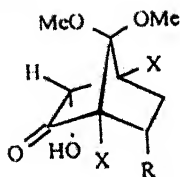
105a Ph, H

105b OEt, H

117 -(CH<sub>2</sub>)<sub>3</sub>-

## List of New Compounds





X=Cl, R

196a Ph

196b OEt

196c CH<sub>2</sub>OAc

196d OAc

196e TMS

196f CO<sub>2</sub>Me

X=Br, R

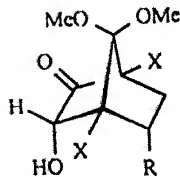
198a Ph

198b OEt

198c CH<sub>2</sub>OAc

198d OAc

198f CO<sub>2</sub>Me



X=Cl, R

197b OEt

197c CH<sub>2</sub>OAc

197d OAc

197e TMS

197f CO<sub>2</sub>Me

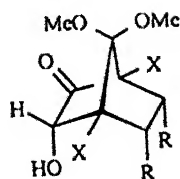
X=Br, R

199b OEt

199c CH<sub>2</sub>OAc

199d OAc

199f CO<sub>2</sub>Me



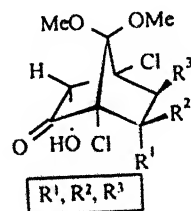
X, R

202i Cl, -(CH<sub>2</sub>)<sub>3</sub>-

202j Cl, -(CH<sub>2</sub>)<sub>4</sub>-

202l Cl, -(CH<sub>2</sub>)<sub>6</sub>-

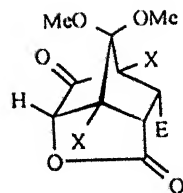
203 Br, -(CH<sub>2</sub>)<sub>4</sub>-



R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>

200b E, H, Me

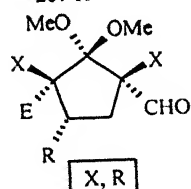
201b Ph, Me, H



X

206 Cl

207 H



X, R

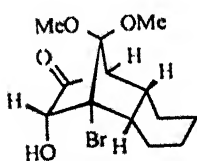
213a Cl, Ph

213b Cl, OEt

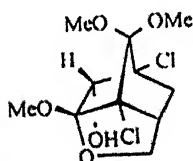
213d Cl, OAc

213e Cl, TMS

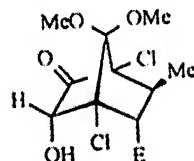
215b Br, OEt



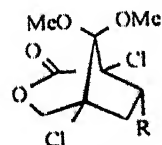
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220

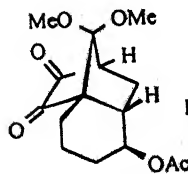


200c



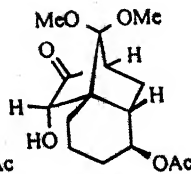
214 R=Ph

221 R=OEt

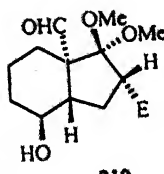


217

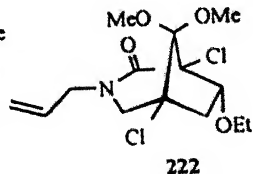
E=CO<sub>2</sub>Me



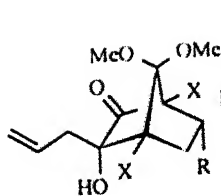
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219



222

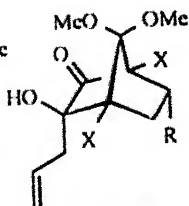


X=Cl, R

238a Ph  
 238b OEt  
 238c CH<sub>2</sub>OAc  
 238d OAc  
 238e TMS  
 238f CO<sub>2</sub>Me

X=Br, R

240a Ph  
 240b OEt  
 240d OAc  
 240f CO<sub>2</sub>Me

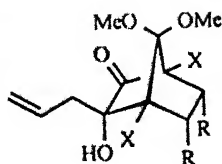


X=Cl, R

239a Ph  
 129b OEt  
 239c CH<sub>2</sub>OAc  
 239d OAc  
 239e TMS  
 239f CO<sub>2</sub>Me

X=Br, R

241a Ph  
 241b OEt  
 240d OAc  
 241f CO<sub>2</sub>Me

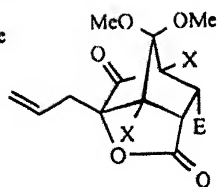


X=Cl, R

246i Cl, -(CH<sub>2</sub>)<sub>3</sub>-  
 246j Cl, -(CH<sub>2</sub>)<sub>4</sub>-  
 246k Cl, -(CH<sub>2</sub>)<sub>5</sub>-  
 246l Cl, -(CH<sub>2</sub>)<sub>6</sub>-  
 246t Cl, -O-(CH<sub>2</sub>)<sub>2</sub>-O-  
 246v Cl, CH<sub>2</sub>OAc

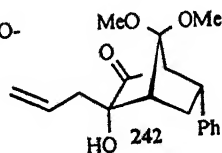
X=Br, R

247i Cl, -(CH<sub>2</sub>)<sub>3</sub>-  
 247j Cl, -(CH<sub>2</sub>)<sub>4</sub>-  
 247k Cl, -(CH<sub>2</sub>)<sub>5</sub>-  
 247t Cl, -O-(CH<sub>2</sub>)<sub>2</sub>-O-  
 247v Cl, CH<sub>2</sub>OAc

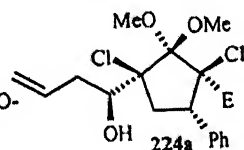


X

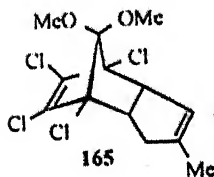
248 Cl  
 249 Br  
 250 H



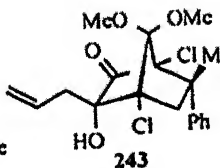
242 Ph



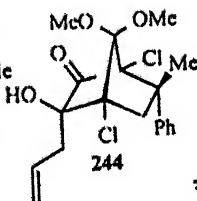
224a Ph



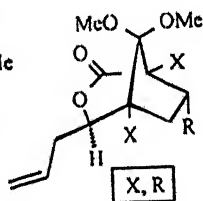
165 Me



243



244



X, R

E=CO<sub>2</sub>Me

223a Cl, Ph  
 223b Cl, OEt  
 225b Br, OEt

# Appendix: A.3 Publications

## JACS COMMUNICATIONS

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### Synthesis of a Novel, Highly Symmetric Bis-Oxa-Bridged Compound

Faiz Ahmed Khan\* and Jyotsimayee Dash

Department of Chemistry, Indian Institute of Technology, Kanpur-208 016, India

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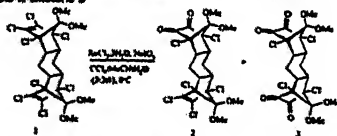
The synthesis and chemistry of aesthetically pleasing, strained polycyclic unsaturated compounds continues to fascinate and pique the imagination of chemists because of their unusual geometries, marvelous structural architectures, and intriguing chemistry, leading to a great deal of physical–organic, theoretical, and spectroscopic investigations.<sup>1</sup> The unforgivable thermodynamic stability due to high strain which poses a formidable synthetic challenge for designing a rational strategy for their creation, generated a lot of interest among synthetic chemists, and culminated in the synthesis of a wide class of strained systems, mostly carbocyclic compounds.<sup>1,2</sup> Another equally enthralling synthetic task is the preparation of relatively less explored bicyclic strained compounds, which have started receiving considerable current interest due to the exciting as well as more useful properties exhibited by them compared to that of carbocyclic analogues.<sup>3</sup> The rigid “heterologues” dotted with heteroatoms such as oxygen, nitrogen, or sulfur but also as prospective building blocks for the synthesis of complex polycyclic unsaturated and natural products.

As a consequence of our ongoing efforts aimed at selective utilization of halogens in Diels–Alder adducts of tetrachloro-5,5-dimethoxybicyclopentadienes,<sup>4,5</sup> we have recognized the feasibility of ruthenium-catalyzed oxidation of 1,2-dichlorobis- $\alpha$ -diketones on a variety of norbornyl derivatives,<sup>6</sup> which have been serving as highly potent and isomeric templates in organic synthesis.<sup>6</sup> We envisioned that a bis- $\alpha$ -diketone (**2**, Scheme 1), prepared using our methodology,<sup>6</sup> would have wide synthetic applications due to its unique topology as well as functional group disposition. We herein report an elegant application wherein a one-pot synthesis of a highly oxygenated strained bis-oxa-bridged compound is delineated from the bis- $\alpha$ -diketone and generalized to other substrates.

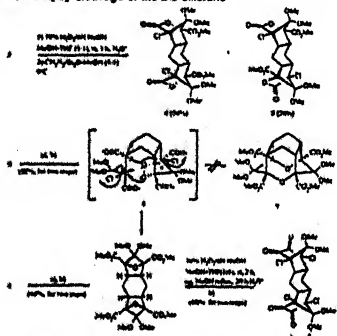
The bis-adduct **1** was prepared by following the literature procedure.<sup>6</sup> We have recently reported that when **1** was subjected to the ruthenium-catalyzed oxidation conditions, either a mixture of mono-diketone **2** (42%) and bis-diketone **3** (10%) or only bis-diketone **3** (63%) were formed, depending on the reaction conditions.<sup>6</sup> At this juncture, we decided to expend efforts to improve the yield of **3** because of its importance as a potential building block. Several rounds of optimization efforts led us to prepare exclusively bis-diketone **3** in quantitative yield simply by adding an aqueous solution of 11%  $\text{RuCl}_3$  and 2.5 equiv of  $\text{NaIO}_4$  in one portion to the substrate in  $\text{MeCN}-\text{CHCl}_3$  at 0 °C (Scheme 1).

The bis-diketone **3** was subjected to a diene cleavage reaction employing alkaline  $\text{H}_2\text{O}_2$ , an efficient method we have recently demonstrated for the cleavage of other norbornyl  $\alpha$ -diketones.<sup>6</sup> Interestingly, the bis-diketone **3** afforded, upon subsequent treatment with diamine, a separable mixture of two products (**4** + **5**) in 74% yield (Scheme 2).<sup>6</sup> The peaks in  $^1\text{H}$  NMR spectra revealed that **4** is less symmetric than **5**. In  $^{13}\text{C}$  NMR, the major compound **4** (54%) showed a 12-line spectrum, while the minor compound **5** (20%) showed an 11-line spectrum. On the basis of the degree of symmetry shown in  $^{13}\text{C}$  NMR, the major compound was unambigu-

**Scheme 1.** Ruthenium-Catalyzed Oxidation of Bis-adduct **1** to Bis- $\alpha$ -diketone **3**



**Scheme 2.** Synthesis of the Novel Bis-bridged Compound **8** via Alkaline  $\text{H}_2\text{O}_2$  Cleavage of the Bis-diketone<sup>6</sup>



\* Reagents and conditions: a) 1)  $\text{NaOH}-\text{MeOH}$ , reflux, 24 h;  $\text{H}_2\text{O}_2$ , 0 °C; b)  $\text{CH}_2\text{N}_2$ ,  $\text{Et}_2\text{O}-\text{MeOH}$  (1:1), 0 °C.

only assigned the  $\alpha$ -symmetric pentacyclic bis-lactone structure **4**. The minor lactone, which is more symmetric, was assigned  $\text{C}_2$ -symmetric pentacyclic bis-lactone **5**.

A careful observation of the structural morphology of the minor  $\text{C}_2$ -symmetric pentacyclic bis-lactone **5** revealed that the intermediate **6**, which would be generated upon treatment of **3** with  $\text{NaOH}$  (Scheme 2), possesses suitably disposed alkoxide moieties that are expected to undergo intramolecular face-to-face  $\text{S}_\text{N}2$  cyclization resulting in a cage compound **7**. On the other hand, a relatively strained bis-oxa-bridged compound **8** would result if the alkoxide moieties displace the respective chlorine atoms present in the same ring. To check the feasibility of this plan, the minor  $\text{C}_2$ -symmetric bis-lactone was refluxed with  $\text{NaOH}$  in aqueous  $\text{MeOH}$  for 24 h. Esterification of the crude product with diamine gave, contrary to our expectations, a strained novel bis-oxa-bridged compound **8** in 52% yield. Both  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra reveal a highly symmetrical structure. The four ester groups appeared as a singlet at 3.80 ppm, while two sets of peaks at 3.44 and 3.31 ppm were

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1015-1018Regio- and Diastereoselective Reduction  
of Nonenolizable  $\alpha$ -Diketones to  
Acyloins Mediated by Indium Metal

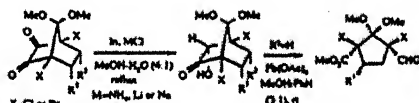
Faiz Ahmed Khan,\* Jyotirmayee Dash, Nilam Sahu, and Sharad Gupta

Department of Chemistry, Indian Institute of Technology, Kanpur-208 016, India

faiz@iitk.ac.in

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## ABSTRACT



$\alpha$ -Diketones are efficiently reduced with indium metal in methanol-water in the presence of  $\text{NH}_4\text{Cl}$ ,  $\text{LiCl}$ , or  $\text{NaCl}$  to give regio- and diastereoselectively the corresponding acyloins in good to excellent yield. The cleavage of the acyloins under  $\text{Pb}(\text{OAc})_2/\text{MeOH-PhH}$  condition provides a convenient and regioselective access to highly functionalized cyclopentane carboxaldehydes, potential building blocks in organic syntheses.

It is well-known that the acyloin ( $\alpha$ -hydroxyketone) functional group plays an important role in organic synthesis and is widespread in compounds of natural origin as well as in advanced intermediates on route to several target molecules.<sup>1</sup> Conventionally,  $\alpha$ -hydroxyketones are prepared by acyloin condensation reaction,<sup>2</sup> oxidation of enolates,<sup>3</sup> and reduction of  $\alpha$ -diketones.<sup>4</sup> However, the problems of over-reduction to a diol<sup>5</sup> or to an  $\alpha$ -methylene ketone<sup>6</sup> that are associated with reduction of  $\alpha$ -diketones make this procedure less attractive. Thallium(III)-promoted  $\alpha$ -oxidation of ketones to  $\alpha$ -acetoxy ketones is the most recent entry<sup>7</sup> to the growing

list. Indium-mediated reactions have gained considerable importance in the recent past due to their mild nature, functional group tolerance, high stereoselectivity, ease of handling, and versatility of the reagent for a number of useful transformations that could be carried out even in water as solvent, without a need to rigorously exclude air.<sup>8</sup> However, there are limited number of reports in the literature on indium-mediated reductions.<sup>9</sup> In continuation of our work on indium-mediated reactions,<sup>10</sup> we report herein a mild, efficient, and stereoselective route to acyloins mediated by indium metal in  $\text{MeOH}$  and water in the presence of  $\text{NH}_4\text{Cl}$ ,  $\text{LiCl}$ , or  $\text{NaCl}$ .

The requisite  $\alpha$ -diketones 1a–26a were prepared efficiently in excellent yields from the readily available Diels–Alder adducts<sup>11</sup> following a methodology developed recently

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(7) Lee, J. C.; Jin, Y. S.; Choi, J.-H. *Chem. Commun.* 2001, 954. (8) (a) Chata, P. *Synlett* 1998, 1067. (b) Chan, T.-H.; Isaac, M. S. *Pure Appl. Chem.* 1994, 66, 919. (c) Marshall, J. A. *Chemtracts* 1997, 10, 481. (d) Hamill, A. S. K. *J. Pract. Chem.* 1998, 140, 84. (e) Li, C.-J.; Chan, T.-H. *Tetrahedron* 1999, 55, 11149.

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An Easy Access to  $\gamma$ -Lactone-Fused CyclopentanoidsFaiz Ahmed Khan,\* Jyotirmayee Dash, Nilam Sahu, and Ch. Sudhakar  
Department of Chemistry, Indian Institute of Technology, Kanpur-208 016, India

faiz@iitk.ac.in

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The tricyclic  $\alpha$ -keto hemiacetals **3a,b** and **3c–d** obtained from ruthenium-catalyzed oxidation of tetrahalonorbornyl derivatives possessing a pendant hydroxymethyl group were cleaved using  $Pb(OAc)_4$  or alkaline  $H_2O_2$  to give  $\gamma$ -lactone-fused cyclopentane derivatives **5a,b** and **5c–d**. The  $\alpha$ -keto hemiacetal **3b** has also been elaborated to spiropodide derivative **25**. The stable hydrate **4** formed from ruthenium-catalyzed oxidation of acrolein adduct **10** furnished an intramolecular hemiacetal **11** upon cleavage with  $Pb(OAc)_4$ . The  $\alpha$ -halo ester moiety in **5a** was transformed smoothly in a highly regio- and stereoselective manner to  $\alpha$ -hydroxy esters through a lactone-assisted intermediate to furnish **18**.

## Introduction

$\gamma$ -Lactone-fused cyclopentanoids are important intermediates in organic synthesis and are among the most abundant substructures found in numerous naturally occurring molecules. A cyclopentane ring cle-fused at the  $\alpha,\beta$ -bond of the  $\gamma$ -lactone is the basic structural unit of many complex and challenging biologically active natural products<sup>1</sup> and also functions as the basic building block for the synthesis of a variety of cyclopentanoid natural products.<sup>2</sup> This provided us the impetus to conceive a convenient and general method for their preparation. Various synthetic methods have been adopted in the literature to acquire this important ring system.<sup>3</sup> However, many of these are target-oriented. We describe herein a novel, short, and efficient methodology to realize the cyclopentanoid  $\gamma$ -lactones making use of the persuasive advantages of the structural flexibility and stereochemical control offered by the tetrahalonorbornene derivatives.<sup>4</sup>

## Results

As a part of our research program on the selective utilization of two sets of halogens (bridgehead vs vinylid)<sup>5</sup>

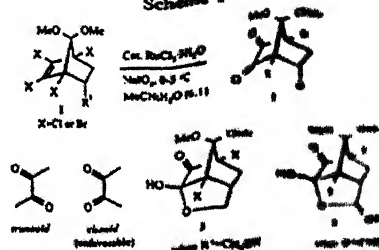
(1) For some recent examples, see: (a) Wang, R.; Shinkai, Y. *J. Chem. Soc., Chem. Commun.* 1999, 413. (b) Huang, J.; Yokoyama, R.; Yang, C.; Fukuyama, Y. *Tetrahedron Lett.* 2000, 41, 6111. (c) Morita, H.; Fujiwara, M.; Nakanishi, Y.; Kobayashi, J. *Tetrahedron* 2000, 56, 5801. (d) Miyake, H.; Tanaka, M.; Yamada, Y. *Tetrahedron* 2000, 56, 5803.

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## Scheme 1



in tetrahalonorbornene derivatives, we have recently recognized the feasibility of ruthenium-catalyzed oxidation of 1,2-dihaloketenes to  $\alpha$ -diketones on a variety of norbornyl derivatives (**1**–**3**),<sup>6</sup> which have been serving as highly potent and inextinguishable templates in organic synthesis. One of the obvious consequences of the geometrical constraints on the  $\alpha$ -diketone moiety in norbornyl derivatives **2** is the imposition of the unfavorable cisoidal conformation, rendering one of the carbonyl groups of  $\alpha$ -diketone to acquire high propensity to interact either with a nucleophilic or electrophilic substituent, which is suitably disposed, to avoid unfavorable electronic interactions. Thus, when the endo-substituent **R'** in **1** is hydroxymethyl, a stable hemiacetal **3** in which one of the carbonyl groups of  $\alpha$ -diketone is attached to a hydroxylated carbon was isolated. On the other hand, an electrophilic endo-substituent (**R'** =  $CHO$ ) promotes the formation of a stable hydrate **4** (Scheme 1).

The tricyclic  $\alpha$ -keto hemiacetals **3** are important not only because of the occurrence of closely related substructure in some of the biologically active natural products<sup>1</sup> but also because they could serve as potential building blocks in organic syntheses. The substrates **3**

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# Rearrangement of 1,4,5,6-tetrahalo-7,7-dimethoxybicyclo[2.2.1]-hept-5-en-2-ones to phenolic derivatives

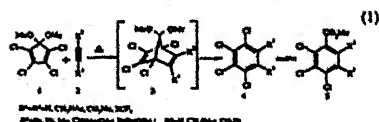
Faiz Ahmed Khan,\* Jyotirmayee Dash, Dhoresaj Jain and R. Prabhudas

Department of Chemistry, Indian Institute of Technology, Kanpur-208 016, India.  
E-mail: faiz@iitk.ac.in

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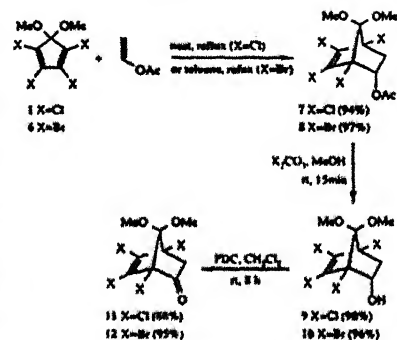
A simple Diels-Alder route leading to methyl 2,3,4-trihalo-5-hydroxybenzoates via thermal Grob-type rearrangement of easily accessible 1,4,5,6-tetrahalo-7,7-dimethoxybicyclo[2.2.1]hept-5-en-2-one with concomitant methyl halide elimination is described.

Benzene and its derivatives are extremely useful starting materials in the synthesis of target molecules of biological and industrial importance.<sup>1</sup> The Friedel-Crafts reaction is one of the fundamental methods<sup>2</sup> for the synthesis of polysubstituted benzenes via stepwise introduction of the substituents into the aromatic ring. The regioselective construction of substituted benzenes requires careful choice of reagents and generally starts from benzenoid precursors. Although cyclotrimerization of alkynes to benzenes was one of the important milestones in the year 1948 (Reppe), it was not until recently that transition-metal mediated/catalyzed approaches for the synthesis of polysubstituted benzene derivatives were considered an attractive alternative.<sup>3</sup> Another possible route to the preparation of substituted benzenes is via extrusion of carbon monoxide<sup>4</sup> or rearrangement<sup>5</sup> reaction of bicyclo[2.2.1]heptene derivatives. Thermal fragmentation of Diels-Alder adducts 3 derived from tetrachloro-5,5-dimethoxycyclopentadiene 1 and acetylenic dienophiles 2 to furnish aromatic products was extensively studied.<sup>6</sup> The norbornadiene derivatives 3 are unstable and undergo aromatization at the temperature at which they are formed, either by extrusion of dimethoxycarbene to give tetrachlorobenzenes 4 or by retaining the bridge carbon to yield aromatic esters 5 [equation (1)]. We herein report a rearrangement of the title compounds 11 and 12 to substituted phenols 13 and 14 [equation (2); see below] and suggest a plausible mechanism for the fragmentation.



## Results and discussion

As part of our ongoing research program directed towards the selective utilization of halogens of tetrahalo-7,7-dimethoxynorbornene derivatives<sup>7</sup> 7 and 8, we prepared the tetrahalodimethoxy-2-ono compounds 11 and 12. They were easily obtained via the sequence depicted in Scheme 1. A Diels-Alder reaction between tetrachloro-5,5-dimethoxycyclopentadiene<sup>8</sup> 1 and vinyl acetate gave the endo-acetate adduct 7 in high yield.<sup>9</sup> Similarly the tetrabromo derivative 3 was prepared in almost quantitative yield by refluxing the tetrabromodimethoxycyclopentadiene 6 and vinyl acetate in toluene. The



Scheme 1

acetate group was hydrolyzed using K<sub>2</sub>CO<sub>3</sub> in MeOH and the resulting secondary alcohols 9 and 10 were oxidized with pyridinium dichromate (PDC) in dichloromethane to furnish the corresponding 2-ono compounds 11 and 12 in excellent yield (Scheme 1).

The endo-acetate adduct 7 has been widely used for applications requiring 7-ono as well as 2-ono derivatives.<sup>10,11</sup> However, in each case the hydrolysis of the 7-ketal or oxidation of the 2-hydroxy group (of 9) was performed only after complete reductive dehalogenation, since the carbonyl group would be expected to react in the reductive dehalogenation step. That means tetrahalo ketones 11 and 12 have remained unexplored so far.

Tetrabromodimethoxynorborn-5-en-2-one 12 was made for the first time following the sequence shown in Scheme 1. After silica gel purification, product 12 was crystallized in hexane to give a white crystalline solid (mp 72–73 °C). The solid, upon storage for 2 days at room temperature, underwent transformation into a hard, powdery solid (mp 193–194 °C). The IR spectrum clearly showed the presence of a hydroxy group (3200 cm<sup>-1</sup>) and an ester (1700 cm<sup>-1</sup>). Based on <sup>1</sup>H and <sup>13</sup>C NMR data the compound was characterized as a phenolic ester derivative 14 [equation (2)]. The rearrangement of 12 was spontaneous when it was heated to 90 °C. The phenolic derivative 14 yielded methyl ether 15 upon treatment

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# A Ruthenium-Catalyzed, Novel and Facile Procedure for the Conversion of Vicinal Dihalalkenes to $\alpha$ -Diketones

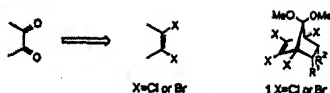
Faiz Ahmed Khan,\* B. Prabhudas, Jyotirmay Dash, and Nilam Sahu

Department of Chemistry, Indian Institute of Technology  
Kanpur-208 016, India

Received June 2, 2000

The plenitude of functional groups along with the vast array of methodologies to create, interconvert, and utilize them in a variety of bond forming reactions serve as an important asset for designing chemical synthesis of any target molecule. The  $\alpha$ -diketones, a powerful assembly of two adjacent carbonyl groups, are of great interest because of their wide-ranging applications.<sup>1</sup>  $\alpha$ -Diketones exhibit interesting photochemistry,<sup>2</sup> are used as flavorants,<sup>3</sup> serve as precursors for ligands in transition metal chemistry,<sup>4</sup> and are used in the preparation of variety of heterocycles<sup>5</sup> and natural products.<sup>6</sup>  $\alpha$ -Diketones also function as the key elements in the Weiss reaction<sup>7</sup> and in the construction of rigid molecular assemblies (molecular wires, rods, etc.) based on "block" chemistry.<sup>8</sup> Some of the common methods to obtain  $\alpha$ -diketones are the following: (i) oxidation of  $\alpha$ -hydroxyketones,<sup>9</sup> (ii) oxidation of alkynes,<sup>10</sup> and (iii) oxidation of  $\alpha$ -methylene ketones.<sup>11</sup> Although controlled oxidation of alkenes is difficult,  $\text{KMnO}_4/\text{Ac}_2\text{O}$  was reported<sup>12</sup> to give low to moderate yields of  $\alpha$ -diketone along with side products. However, the method is not suitable for small cyclic (below cyclooctane) and bicyclic systems. It transpired to us that vicinal dihaloalkenes could serve as masked  $\alpha$ -diketones (Scheme 1).<sup>13</sup> We particularly chose easily

Scheme 1



accessible<sup>14</sup> substrates 1 because the tetrachloro derivatives of 1 have been serving as exceptionally powerful templates for the synthesis of numerous complex natural as well as aesthetically pleasing unnatural products.<sup>15</sup> A careful literature search revealed that the vicinal dihaloalkene moiety in 1 is quite robust and unreactive toward several reagents,<sup>16</sup> including  $\text{OsO}_4$  oxidation conditions.<sup>17</sup> It is interesting to note that the presence of halogens in 1 is rather a compulsion than choice<sup>18</sup> and a complete reductive dehalogenation is almost invariably followed. We recently reported selective utilization of halogens in 1 for C–C bond formation at the bridgehead.<sup>19</sup> In continuation of our efforts to use halogens in 1 as useful functional groups, we developed a novel, facile, and extremely efficient methodology employing catalytic  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}$  and  $\text{NaIO}_4$  as stoichiometric oxidant<sup>20</sup> and report herein our results.

The substrates 1a–21a were subjected to ruthenium tetroxide (generated in situ) oxidation employing  $\text{RuCl}_3 \cdot 3\text{H}_2\text{O}/\text{NaIO}_4$  in acetonitrile–water (6:1). The results are summarized in Table 1. In all the cases the reaction proceeds smoothly and efficiently, providing good to excellent yield of crystalline, yellow  $\alpha$ -diketones (entries 1–6, 13–18) or the products derived from them (entries 7–12, 19–21).<sup>20</sup> Reaction times varied considerably, but in general tetrabromo derivatives required relatively longer time compared with tetrachloro derivatives and so is the case with disubstituted versus monosubstituted ( $R^2 = \text{H}$ ) derivatives in each series. It is interesting to note that only one of the two primary hydroxyl groups in 7a and 19a was partially affected, forming aldehyde first, followed by lactol formation and further oxidation to furnish lactones 7c and 19c. While the lactol thus formed is responsible for hemiacetals 7d and 19d. The symmetric bis lactones 7e and 19e originate from the glycol cleavage of the intermediates 7f and 19f. On the other hand, mono-hydroxy-methyl-substituted derivatives 8a and 20a exclusively furnished the corresponding hemiacetals in high yields. The acid 9a also gave a similar result. Protection of hydroxyl groups in all these cases furnished the normal  $\alpha$ -diketone product (entries 3, 15, and 18). It is remarkable to note that the conversion of sensitive substrates 6a and 17a was smoothly accomplished in excellent yield.

- (14) Substrates 1 were obtained via Diels–Alder reaction of 1,2,3,4-tetrahalo-5,5-dimethylcyclopentadiene with a series of dienophiles, see: McBee, E. T.; Divisley, W. R.; Burch, J. E. *J. Am. Chem. Soc.* 1955, 77, 3853–387. Onabekhe, A. S. *Diene Synthesis*; Int. program for scientific translation, Jerusalem, 1964. Pews, R. G.; Roberts, C. W.; Hand, C. R. *Tetrahedron* 1976, 26, 1711–1717. In some cases routine functional group manipulations of the initial adduct furnished the desired substrate. Full details of the new adducts reported here will be published in a full account soon.
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- (20) All new compounds were satisfactorily characterized by spectroscopic methods including elemental analysis.

## THE REAGENT

## 1,2,3,4-Tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene: Diels-Alder Reactions and Applications of the Products Formed

Fate Ahmed Khan,\* B. Prabhadas, and Jyotirmayee Dash

Kanpur (India), Department of Chemistry, Indian Institute of Technology

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**Keywords:** Cycloadditions, Cyclopentadienes, Natural products, Reagents, Diels-Alder Reactions

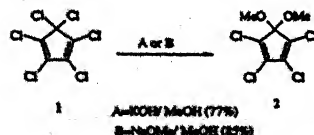
**Abstract.** Readily available 1,2,3,4-tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene (**2**) is an excellent cyclic diene for Diels-Alder reaction with a vast variety of dienophiles. The products so formed (norbornene derivatives) constitute important building blocks for the synthesis of diverse complex natural as well as non-natural products. Apart from very high *endo* selectivity associated with Diels-Alder reactions, there are several other fascinating features associated with these

bicyclic products which make them convenient entities in the synthesis of complex molecules. The most important is the rigid framework that act as a powerful template to provide high degree of selectivity and directional nature to various substituents. The proposed article is intended to focus on Diels-Alder reactions of **2** and the applications of norbornene derivatives in organic synthesis.

## Contents

1. Diels-Alder Reactions of 1,2,3,4-Tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene
2. Application in the Synthesis of Natural Products and their Intermediates
3. Application in the Synthesis of Unnatural Products
4. Miscellaneous

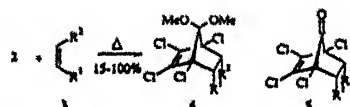
The preparation of 1,2,3,4-tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene (**2**) was first reported by Newcomer and McBee in 1949 [1a]. The addition of KOH-MeOH [1] or NaOMe-MeOH [2] to the easily available hexachlorocyclopentadiene (**1**) affords **2**, the yellow coloured liquid having sweet odour. This cyclic electron deficient diene **2** has been successfully utilized as an excellent reactant in numerous Diels-Alder reactions with a wide variety of dienophiles possessing both electron rich and electron deficient groups under mild conditions. Apart from high *endo* selectivity associated with the products so formed, the diene **2** can serve as masked cyclopentadienones, which is not a suitable candidate for the Diels-Alder reaction as it undergoes dimerisation.



## 1. Diels-Alder Reactions of 1,2,3,4-Tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene

Diels-Alder reaction is one of the most important and fundamental carbon-carbon bond forming reaction for the construction of six membered carbocycles. The Diels-Alder reaction

of **2** with maleic anhydride was first demonstrated by Newcomer and McBee [1]. Subsequently the remarkable reactivity of this diene **2** in Diels-Alder reactions with a variety of electron rich and electron deficient olefinic dienophiles [3–8] was thoroughly investigated by McBee [3] and then by Hoch [4] and Jung, [5] exclusively giving rise to the *endo* adducts **4**. The adducts **4**, in majority of the cases, provide a convenient route to the synthesis of bicyclic bridged ketones **5** upon treatment with conc.  $\text{H}_2\text{SO}_4$  [3, 5, 7a] which are potential synthetic intermediates leading to diverse carbocyclic skeletons.

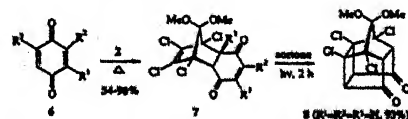


$\text{R}^1 = \text{H, Me, Hapt, CO}_2\text{Me, COMe, CO}_2\text{Me, Ph, CN, OEt, OAc, PhON(OMe)}_2$   
 $\text{Cl, CH}_2\text{Hal (Hal = Cl, Br)}$

$\text{R}^2 = \text{H, Me, CH}_2\text{Cl, Cl}$

$\text{R}^1, \text{R}^2 = \text{C}(\text{O})(\text{CH}_3)_2$  ( $x = 2, 3$ ), Indene, Acenaphthalene

The [4+2] cycloaddition of **2** with quinones **6** proceeds smoothly giving rise to the *endo* adducts **7** [9]. However, **2** remains unreactive with chloranil and 2,5-dichloroquinone [9a]. The adduct **7a** photocyclized to give the cage compound **8** [9c].



$\text{R}^1 = \text{H, Cl, OMe, Ph; R}^2 = \text{H, Cl; R}^3 = \text{H, Me}$

## Appendix: A.4 Resume

### Jyotirmayee Dash

Graduate Student  
Dept. of chemistry  
Indian Institute of Technology Kanpur-208016, India  
Phone: 91-512-597421  
Fax: 91-512-250007  
Email: jdash@iitk.ac.in, jhillu.76@yahoo.co.in

**Permanent address:**  
c/o Basant Kumar Dash  
At. Palada  
P.O./Dist. Jagatsinghpur,  
754103, ORISSA  
Phone: 06724-221916

**Personal:**  
*Date of birth* July 09, 1976  
*Nationality* Indian  
*Hobbies* Writing short stories, poems

#### Educational Qualifications:

Ph.D.	1998-present/CPI 9.33/10 (Thesis submitted) Organic Chemistry Indian Institute of Technology, Kanpur
M. Sc.	1995-1997/1st class, 2 <sup>nd</sup> rank, 76.7% Organic Chemistry (special) Ravenshaw Govt. Auto. College, Cuttack
B. Sc.	1992-1995/1st class, distinction, 73.1% P.C.M.(Chemistry, Honours) Swami Vivekanand Memorial College Utkal University, Bhubaneswar
10+2	1990-1992/ 1st class, 67.3% Swami Vivekanand Memorial College, Jagatsinghpur, Utkal Univ., Bhubaneswar
10 <sup>th</sup>	1990-1992/ 1st class, 81.7% Tarikund High School, Jagatsinghpur C.H.S.E., ORISSA

#### Doctoral Details:

*Title of Thesis* Norbornyl  $\alpha$ -diketones as Important  
Building Blocks in Organic Synthesis

**List of Publications:**

- 1) 1,2,3,4-Tetrachloro-5,5-dimethoxy-cyclopenta-1,3-diene:  
Diels-Alder Reactions and Applications of the Products  
Formed  
F. A. Khan, B. Prabhudas, J. Dash *J. Prakt. Chem.* **2000**,  
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- 3) Rearrangement of 1,4,5,6-tetrahalo-7,7-  
dimethoxybicyclo[2.2.1]hept-5-ene-2-one to Phenolic  
Derivatives  
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- 4) Synthesis of a Novel, Highly Symmetric Bis-Oxa-Bridged  
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- 6) An Easy Access to  $\gamma$ -Lactone-fused Cyclopentanoids  
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Chem.*, **2002**, 67, 3783-3787.
- 7) Synthesis of Novel Caged Bishemiacetals and Their Facile  
Conversion to Symmetric Bis- $\alpha$ -halo- $\gamma$ -lactones  
F. A. Khan, N. Sahu, J. Dash and B. Prabhudas, *J. Ind. Inst.  
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